

The Science of BPA

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Introduction to Session

Problem: lack of early identification of developmental effects of chemicals

Culture Clash: regulatory science vs research science

How can we improve risk assessment approaches? NAS recommendations and other opportunities

What do we need to prove “a reasonable certainty of no harm”?

Early signals from human studies.....



Problem

Examples of “late lessons”

- POPs (DDTs, PCBs, dioxins, PBDEs, PFCs, and potentially new ones on the horizon), many associated with developmental effects that were not predicted with standardized toxicity tests OR were originally introduced without testing and “grandfathered in”
- Metals: Pb, Hg, As, Cd, Mn. Toxicity poorly predicted with animal models

Often regulatory tests have not addressed hazard ID/dose at tissue level

Often regulatory tests have not addressed relevant endpoints (like sexually dimorphic behavior) Weak governmental authorities

EPA, FDA laws “grandfathered in” numerous chemicals, food additives and weakly regulated new chemicals, cosmetics



Caveats

By definition, any adverse effect of a chemical that I – or any epidemiologist – can identify in a human population, reflects a failure in the regulatory system

Premise: the purpose of chemical and product regulation is to predict adverse effects on human health or the environment so that such effects can be prevented

Public health!

Real world: very difficult decisions:



Clash of Cultures: Regulatory Science vs. Research Science

Regulatory science

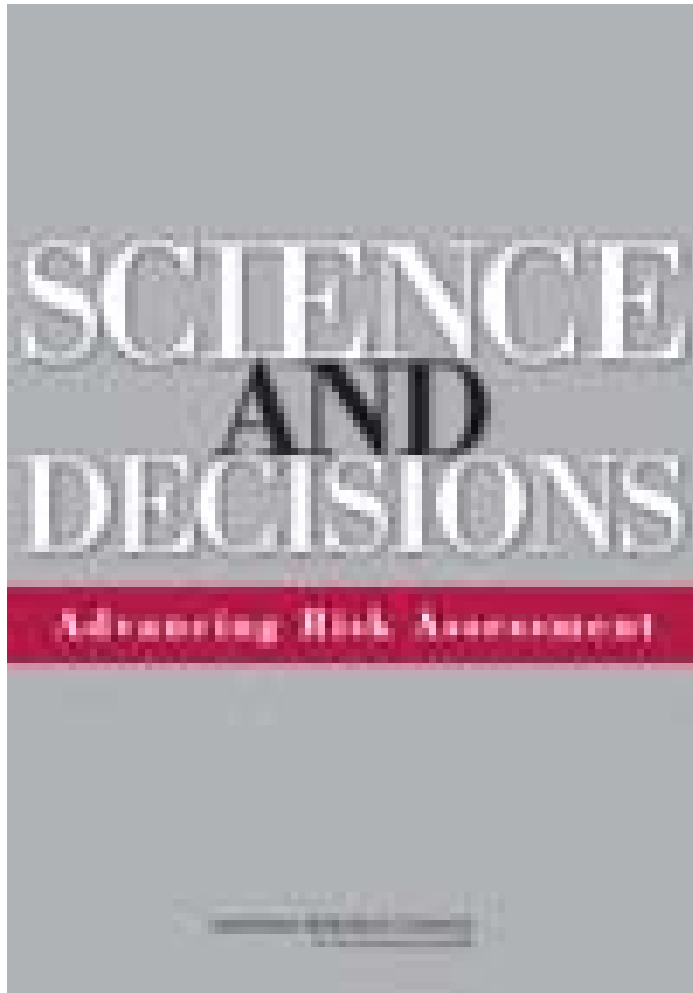
- Goal is to establish a “safe” level with adequate margins of exposure to protect health
- Standardized
- Stable suite of protocols over years
- Methodical step by step approach
- Results are comparable/amenable to risk/risk tradeoffs
- Aims to answer questions about “real world” exposures
- Consensual process with industry in developing standards and need for international harmonization

Research science

- Goal is to establish underlying mechanisms of health/disease/enviro processes
- Creative/inventive
- Constant evolution of assays and tools
- “Hot pursuit” approach to answer fundamental questions
- Results often not comparable
- Not necessarily reflective of real world exposure levels and routes
- Quality judged on the basis of peer review



NAS Science and Decisions: 2009



Risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk rather than as an end in itself.

Improvements in uncertainty and variability analysis and for a unified approach to dose-response assessment that will result in risk estimates for both cancer and noncancer end points.



Science and Uncertainty Report: Scientific Recommendations

- More careful design of risk assessment in its formative stages is needed.
- Characterize and communicate uncertainty and variability in all key steps of risk assessment
- Use of the best, most current science to support and revise default assumptions, explicitly stated defaults, standards for evidence to alternative assumptions
- Use a unified dose-response assessment framework that includes a systematic evaluation of background exposures and disease processes, possible vulnerable populations, and modes of action that may affect human dose-response relationships
- Incorporate interactions between chemical and nonchemical stressors in assessments



Unified dose response framework

- Noncancer effects do not necessarily have a threshold, or low-dose nonlinearity, and the mode of action of carcinogens varies
- Background exposures and underlying disease processes contribute to population background risk and can lead to linearity at the population doses of concern.
- Risk assessments need to more explicitly account for differences among humans in susceptibility including early-life susceptibility



Changes to implement unified dose response framework

- Use of a spectrum of data from human, animal, mechanistic, and other relevant studies;
- A probabilistic characterization of risk;
- Explicit consideration of human heterogeneity (including age, sex, and health status) for both cancer and noncancer end points;
- Characterization (through distributions to the extent possible) of the most important uncertainties for cancer and noncancer end points;
- Evaluation of background exposure and susceptibility;
- Use of probabilistic distributions instead of uncertainty factors when possible;
- Characterization of sensitive populations



Making Research More Relevant to Public Health Decisionmaking (1)

For toxicity studies:

- Relevance of dosing routes to real world exposure
- Relevance of dosing levels to real world exposure
- Numbers and spacing of dosing groups
- Adequate numbers of animals in groups
- Appropriate attention to variability, e.g., inter-individual within species/strains, litter effects and other sources of variability like diets, handler effects, and so forth
- Relevance of endpoints/markers to human health
- Development of relevant PBPK data to understand tissue exposures of chemicals
- GLP certification for research labs



Making Research More Relevant to Public Health Decisionmaking (1)

For epidemiology/field studies:

- Dose response assessment (do it, don't assume linearity)
- Standard deviations (report them please)
- Exposure measurements and reporting of exposure levels
- Addressing confounding among multiple chemical as well as nonchemical exposures (e.g., poor nutrition, stress, pharmaceuticals). Caveat: the multiple exposures that are important are the ones that actually are occurring to real people/the environment.
- Addressing important subpopulations e.g. women with PCOS



Science of BPA: Different Standards

“Standard” for action differs according to statutes:

BPA in chemicals, *“avoid unreasonable risk to health or the environment”*

BPA in infant toys, CPSC *“product presents an unreasonable risk of injury ; injury = death, personal injury, or serious or frequent illness”*

BPA in medical devices

(1) **safe**: reasonable assurance of safety that the probable benefits to health that result from use of the device as directed by the manufacturer outweigh any probable risks

(2) **effective**: based upon valid scientific evidence, the use of the device in the target population according to the manufacturer’s instructions will provide clinically significant results

BPA in food additives, *“Reasonable certainty of no harm under normal conditions of use”*



Science of BPA: exposure scenarios

Routes:

CPSC and food additives: *oral*

Medical devices: *parenteral*

EPA: *oral, dermal, inhalational, non-human (environmental) exposures*

Timing:

“Susceptible” life stages: *adult, infant, in utero (via mother)*

Chronicity: *acute (developmental), subchronic (developmental), chronic (lifetime)*



Science of BPA: Assessment of Low Dose Effects

US NTP “Low Dose” workshop in 2001 was a good first step in identifying:

- Existence of “low dose” effects
- Not all dose responses are monotonic
- Need for new statistical approaches to dose response

Risk assessors do not have appropriate tools for addressing such effects

Many issues from 2001 workshop and similar efforts are still not addressed, e.g., differential species/strain sensitivities, confounding effects of animal feeds, questionable methods for statistical analysis of data, definitions of “adverse effects”



NTP Panel's Conclusions on BPA

From the rodent studies we can conclude that bisphenol A **does change the age of puberty** in male or female rats at **high doses** (ca. **475 mg/kg/day**).

Rodent studies suggest that bisphenol A **causes neural and behavioral alterations** related to disruptions in normal sex differences in rats and mice. (**0.01–0.2 mg/kg/day**). *

There is **sufficient evidence** in rats and mice that bisphenol A **causes female reproductive toxicity** with **subchronic or chronic oral exposures** with a NOAEL of 47.5 mg/kg bw/day and a LOAEL of **>=475 mg/kg bw/day**.

There is **sufficient evidence** in rats and mice that bisphenol A **causes male reproductive toxicity** with **subchronic or chronic oral exposures** with a NOAEL of 4.75 mg/kg bw/day and a LOAEL of **>=47.5 mg/kg bw/day**.



Non Human Primate Studies

Study	Dosing	Endpoint
Leranth 2008	40-400 µg/kg bw/day Parenteral	Decrease in estrogen related synaptogenesis in brains, dose related
Nakagimi 2009	20 µg/kg bw/day BPA Parenteral	Altered maternal and neonatal behavior



Recent Human Studies

Study	Exposure	Outcome
1. Lang 2008 2. Melzer 2009	Urine Metabolite	1. Diabetes 2. Heart Disease
Braun 2009	Urine Metabolite (Pregnant moms)	Disruption of sex differences in externalizing behavior (kids)
Li 2009	Work Area, probably high, maybe mixed	Increased sexual dysfunction in male workers



Much research is under way

FDA/NTP:

Comparative pharmacokinetics of BPA with oral dosing in rodents vs. nonhuman primates using radiolabelled BPA

? Ability of neonate to conjugate BPA

? Role of enterohepatic circulation in increasing exposures to BPA in rodents

Neurotoxicity of BPA with oral dosing

NIEHS:

Significant research investment: reproductive, metabolic, neurologic effects of BPA, hormonal and epigenetic mechanisms, animals and humans



Questions:

- How to make decisions in rapidly shifting landscape of new risk assessment paradigms as well as new data on BPA emerging every day?
- How to appropriately address “low dose” effects?
- Appropriateness of various animal models as surrogates for humans in evaluating endpoints on prenatal programming; how to merge the sciences of endocrinology and developmental biology with the science of toxicology?

