



Commentary

Richard A. Becker, Ph.D. DABT

American Chemistry Council

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A cause without a disease

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Endocrine-disrupting chemicals have become a topic of public concern because they could potentially cause cancer and male infertility. But evidence for a human health problem is hard to find. *Holger Breithaupt*



Commentary

What events or actions catalyzed such an article?
What can be learned and applied as scientific investigations go forward?

Endocrine Research

Are there environmental exposures to hormonally active agents that adversely affect the health of humans?

- Hundreds if not thousands of research studies
- The breadth of is impressive
- Significant number of excellent reviews
 - The number and depth of reviews is notable
- Numerous Nat'l & Internat'l Scientific Mtngs
 - IUPAC
 - MOE
 - Tox Forum
 - OECD

Research Reviews Published

- The National Research Council of the US (1999)
- Endocrine Disruptor Screening and Testing Advisory Committee (U.S. EPA, 1998)
- European Union (1999)
- Environment Canada (1999)
- The Society for Environmental Toxicology and Chemistry (SETAC) (1998, 1999)
- The International Union of Pure and Applied Chemistry (IUPAC) (2003)
- The International Programme for Chemical Safety (IPSC) (2002)

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Catalyzing Action - Early Claims of Synergy: Subsequently Shown to be Scientific Misconduct

- 1996 report in *Science*: claimed immense synergy of “endocrine active” substances

Learned: Don't rush to conclusions based on a single study

Novel findings require corroboration

- Investigation: US Dept of Health & Human Services cited Arnold for “Scientific Misconduct”
 - “Intentional falsifying the research results”
 - “there is no original data or other corroborating evidence to support the research results & conclusions reported in the *Science* paper as a whole

Catalyzing Action: Claims of Effects at Ultra Low Doses

- Some reports of effects at exceedingly low dose levels that don't follow a classical dose-response (vom Saal & co-authors)
- Numerous attempts to corroborate results in different labs (similar methods/models) without success (Ashby)
- Larger scale studies conducted (in some cases different models) with sig. increased power – yet ultra low dose effects not observed (Cagen/Tyl/Japanese govt lab)
- Comprehensive review of Low-Dose results (NTP Report of the Endocrine Disruptors Low-Dose Peer Review, August 2001)

Learned:

- Some have Questioned - Is it real? -
 - Ultra Low Dose effects - if occurring – are not robust
 - Must Evaluate Scientific Evidence in Totality
-
- **EPA CONCLUDED:** “Until there is an improved scientific understanding of the low-dose hypothesis, EPA believes that it would be premature to require routine testing of substances for low-dose effects, March 2002”

Catalyzing Action: Not Fully Participating in Scientific Dialogs & Independent Reviews

Learned:

“Failures in the past to provide full and complete data sets for expert panel analysis cannot be perpetuated, because such actions impact the integrity and credibility of the research.”

Executive Summary IUPAC Symposium
Yokohama Nov. 2002. Pure Appl. Chem.
75 (11/12), 2003



Learned:

Test Methods Must Be Validated

- Standardization & validation of new & significantly revised methods are necessary
- Validation provides the means to understand the reliability of a test method over time and across different laboratories
- Validation provides the knowledge to interpret test results

Learned: Critically Important to Diligently Follow the Scientific Method

“The field of ED is rich with unexpected observations However the science will be aided by a renewed commitment of researchers to follow the scientific method, by testing hypotheses, confirming unexpected findings (wherever possible before publication), communicating data and results clearly, and including in analyses several alternative, biologically plausible reasonable explanations for observations.”

Executive Summary IUPAC Symposium
Yokohama Nov. 2002. Pure Appl. Chem.
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Catalyzing Action: WHO/IPCS Framework

International Programme for Chemical Safety 2002

- WHO/IPCS - a framework to evaluate linkages between exposures to an agent and a particular health outcome
 - Hypothesis – idea underlying the investigation
 - Biological plausibility
 - Strength of the association (dose response)
 - Time of exposure in relation to outcome
 - Consistency across studies (reproducibility)

Learned - it is Appropriate & Scientifically Sound to Apply the Principles of Toxicology and Risk Assessment to Evaluations of Endocrine Active Substances

Risk or Safety = f Hazard, Dose, and Exposure

- Hazard - What effects does the agent cause? Are there stages of differential sensitivity?
- Dose - How potent is it? Different susceptibilities?
- Exposure - What is the exposure to people or the species of concern?
- Weight of the Evidence:
 - **evaluating quality of each study**
 - **strength of findings**
 - **certainties & uncertainties**
 - **integrating all studies**

WHO/IPCS Case Studies

- Breast cancer & exposure to DDE (the main metabolite of DDT)
 - ‘Strong evidence of no relationship’
- PCBs & PAHs & thyroid related effects on neurodevelopment
 - ‘biologically plausible but not sufficiently consistent’
- Atrazine and adverse effects in amphibians
 - ‘no evidence of consistent reproducible findings, lack of biological plausibility & temporal relationship (field studies)’

WHO/IPCS : Sperm Effects

Hypothesis Examined: Global reduction in human semen quality over time are related to increasing exposure to estrogenic, anti-androgenic (identity unknown), or other as yet unidentified chemicals, during critical phases of testicular development

Overall Strength of Evidence -- as concluded by the IPCS expert panel

| <u>Outcome</u> | <u>Hypothesis</u> | <u>EDC mechanism</u> |
|----------------|-------------------------|----------------------|
| Weak | No Relevant Data | Weak |

Catalyzing Action: IUPAC Review

SCIENTIFIC COMMITTEE ON PROBLEMS OF THE ENVIRONMENT
AND
INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

Implications of Endocrine Active Substances for Humans and Wildlife: Executive Summary

J. Miyamoto and J. Burger (Editors)

Associate Editors

John Ashby, William Ecker, Werner Klein, Kenneth Korach,
James Lamb, and Peter Matthiessen



Preferred citation: J. Miyamoto and J. Burger (Eds.)
Implications of Endocrine Active Substances for Humans and Wildlife, SCOPE/ITC/PAC,
Research Triangle Park, NC (2005). <www.iupac.org/publications/pac/2005/9841/>

*“too early to reach firm conclusions ...
...reassuring that after substantial research in the past decade, there have been no conclusive findings of low level environmental exposures to EASs causing human disease.”*

Important to Apply the Lessons Learned & Continue with:

- Coordinated international efforts to standardize and validate test methods and to establish a system for screening and testing substances
- Research to address the areas of concern to enhance overall scientific understanding
- Employing risk assessment framework to place potential exposures within a health context

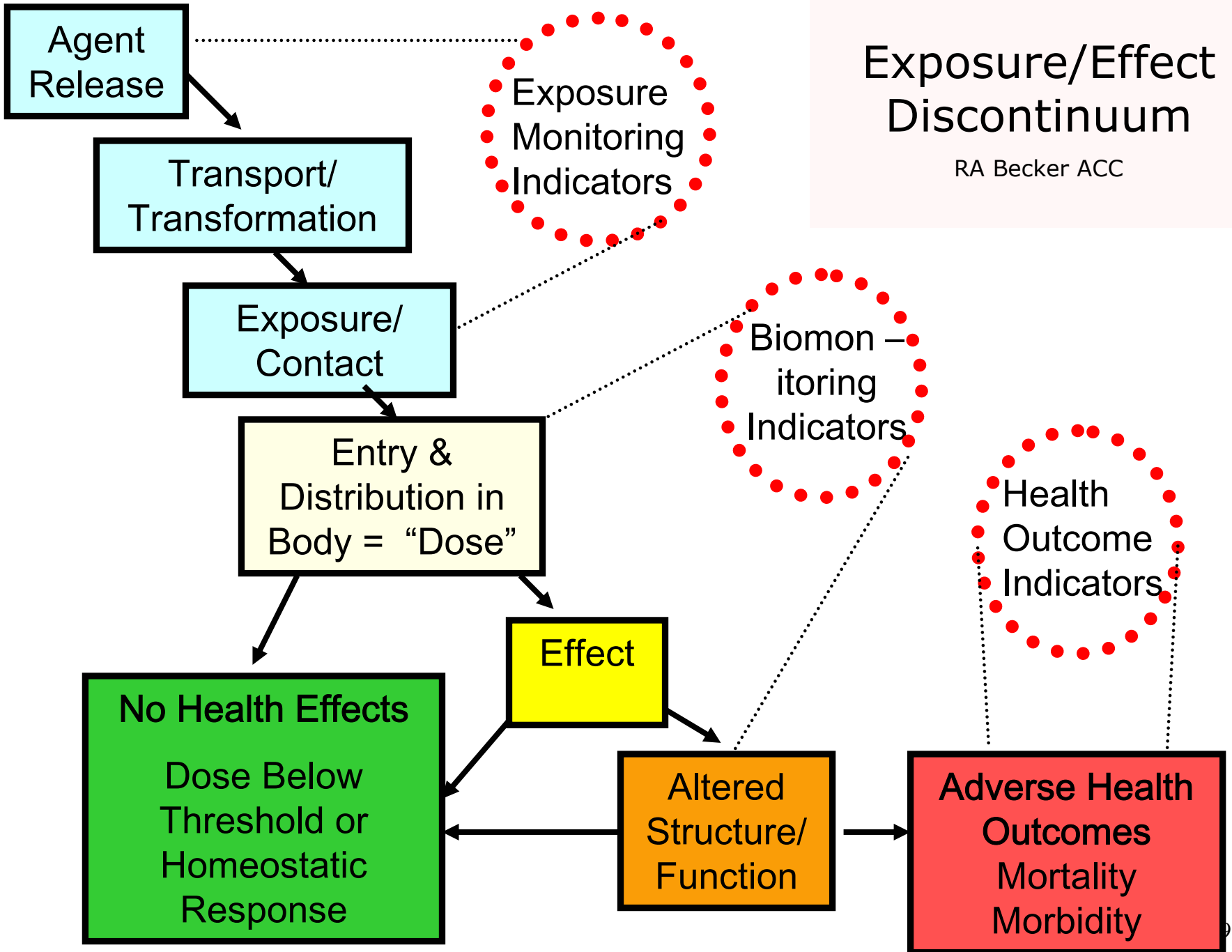
Biomonitoring

Biomonitoring is the measurement of specific substances in the human body, usually through the analysis of blood, urine, breast milk and tissue samples. Typically, biomonitoring studies rely on volunteers to provide samples of fluid and/or tissue at a single point in time. Samples are then analyzed to measure concentrations substances that may be present in the body.

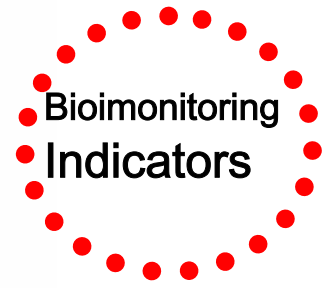
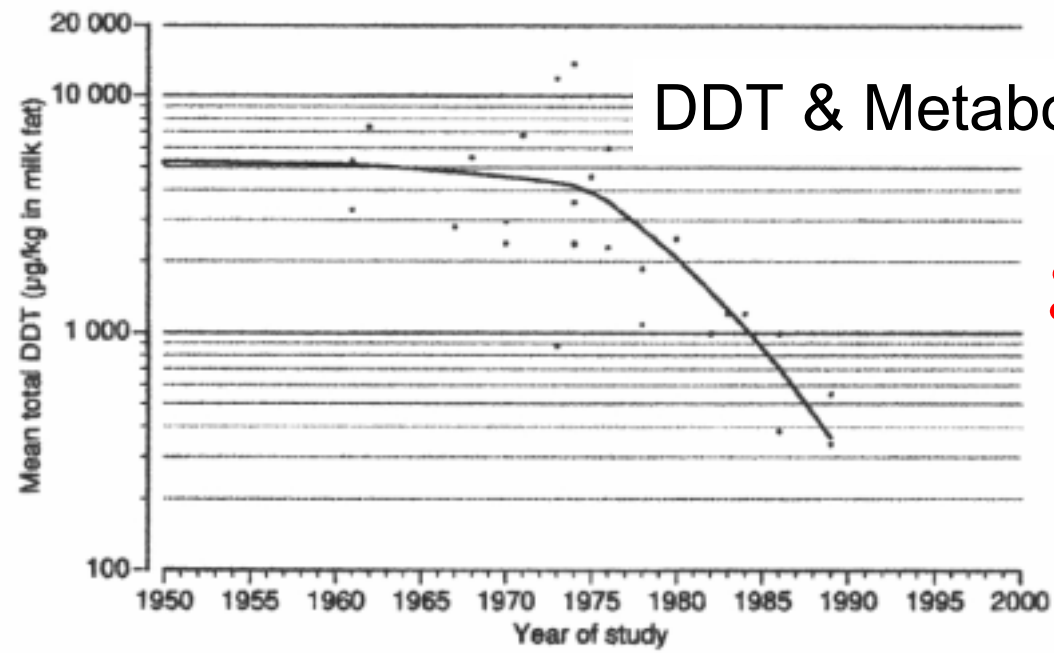
- **The detection of a substance in the body indicates only that an exposure has taken place; it does not indicate whether an exposure has resulted in any adverse health effect.**
- **CDC “Just because people have an environmental chemical in their blood or urine does not mean that the chemical causes disease”**

Exposure/Effect Discontinuum

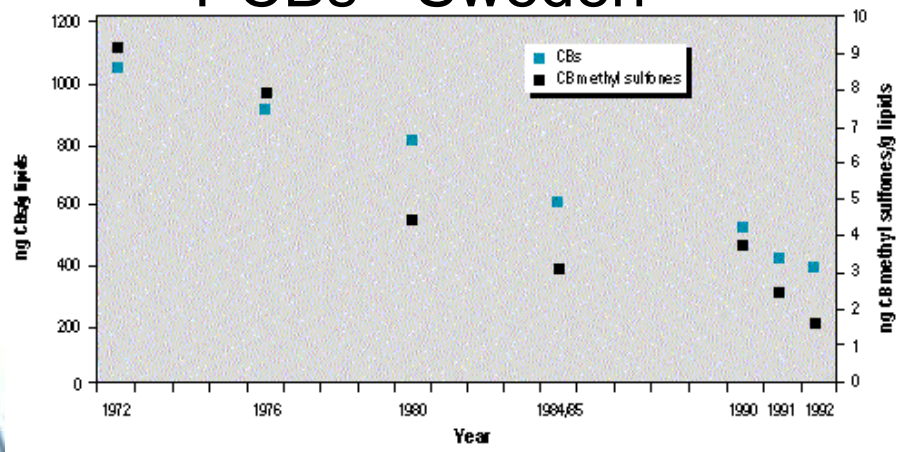
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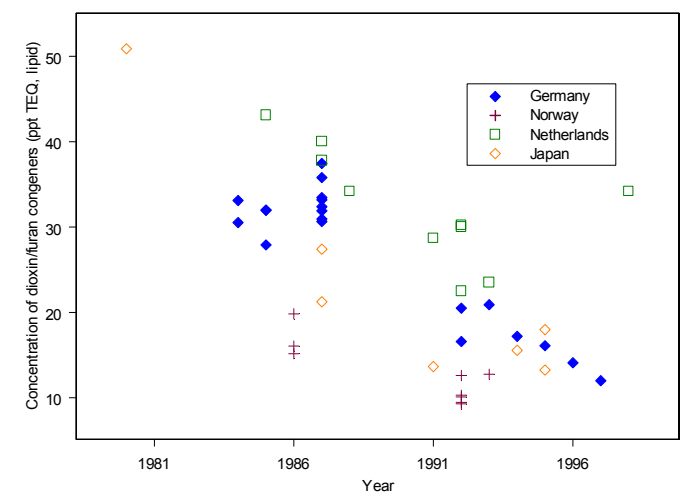
Substances in Human Milk



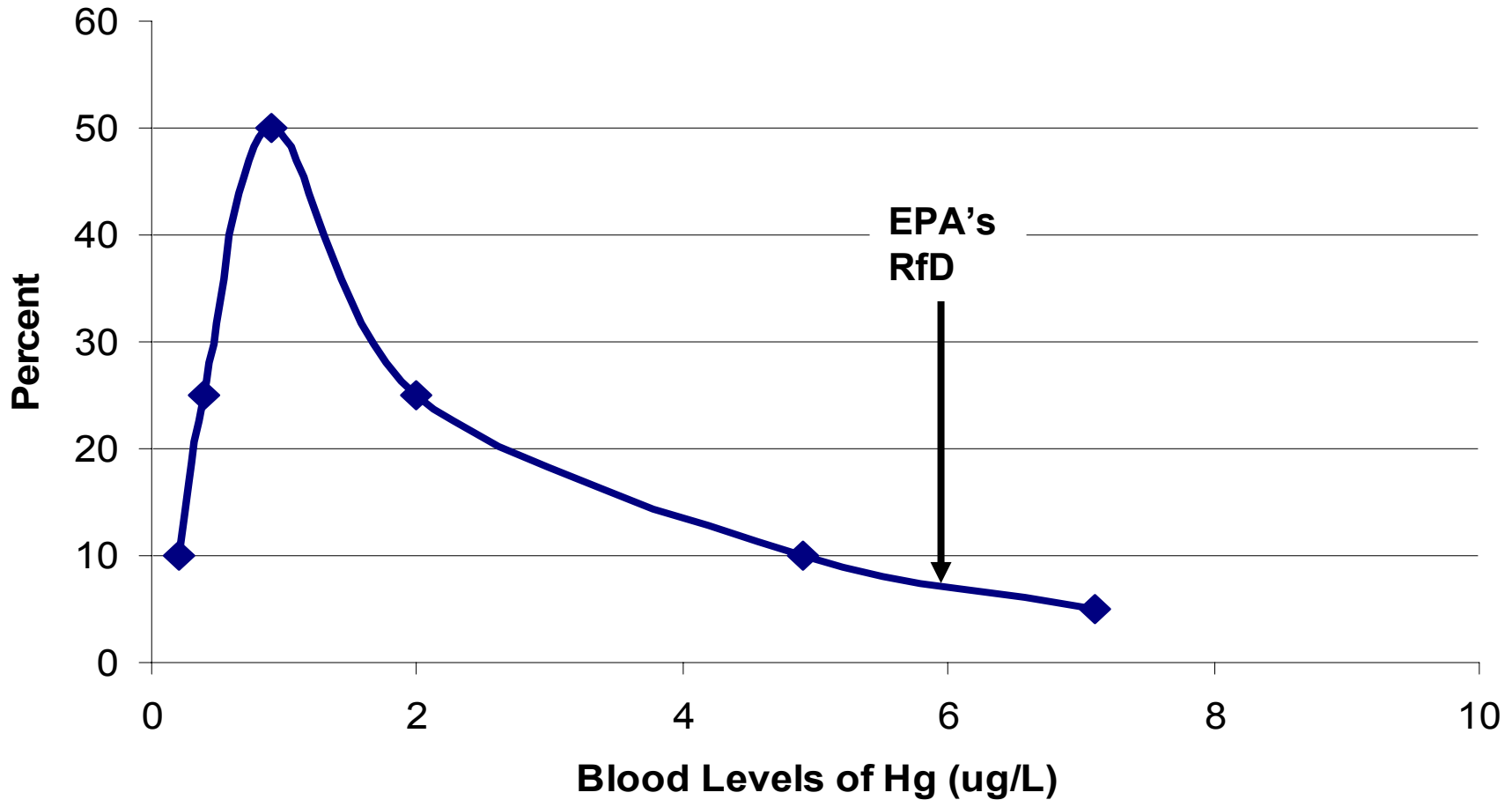
PCBs - Sweden



PCDDs/PCDFS



Population Distribution of Blood Hg Levels in US Women of Childbearing Age



Conclusions Relevant to Biomonitoring

- Presence of a substance \neq Health Risk
- Commitment to the Scientific Method – the WHO/IPCS Framework applies to interpreting biomonitoring results:
 - Hypothesis – idea underlying the investigation
 - Biological plausibility
 - Strength of the association (dose response)
 - Time of exposure in relation to outcome
 - Consistency across studies (reproducibility)
- Production of toxicity in lab animal studies does not mean that humans exposed to lower levels have the same risk for developing disease
- Need standardized & validated methods (+QA/QC)
- Need to relate levels of exposure in humans to the levels that produce effects

Thank You for
Your Attention

Population Distribution of Blood Hg Levels in US Women of Childbearing Age

