



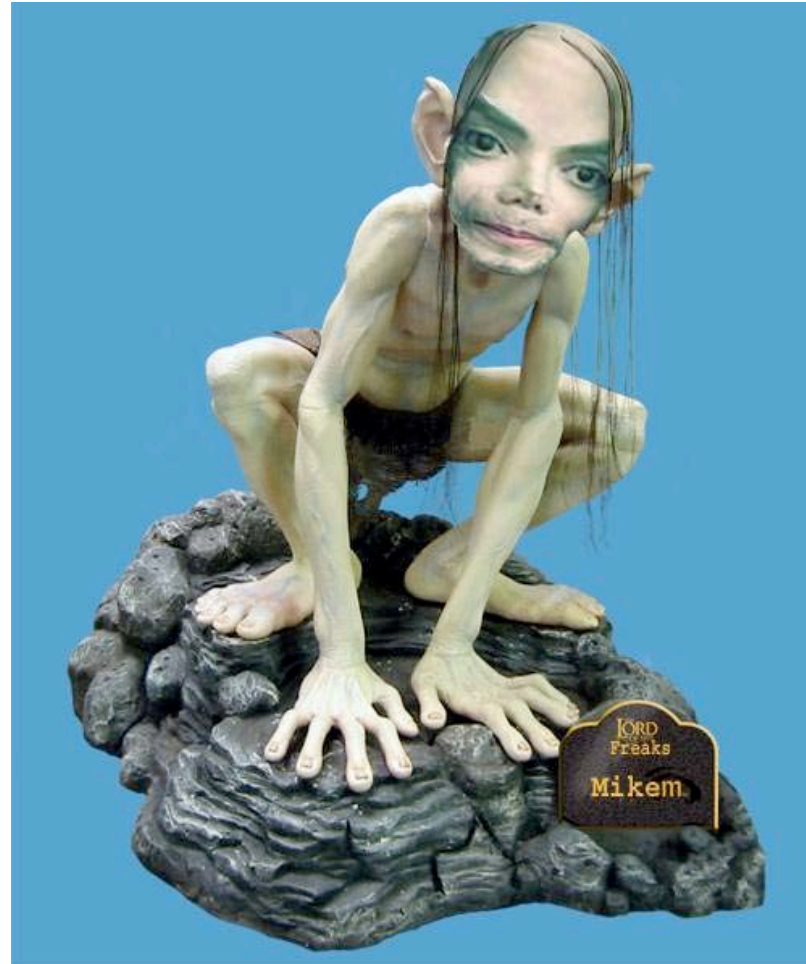
Human Biomonitoring: An Overview

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IS RTP Workshop
“Understanding Human Biomonitoring”

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Xenobiotics: Friend or Foe?



Biomonitoring in the News

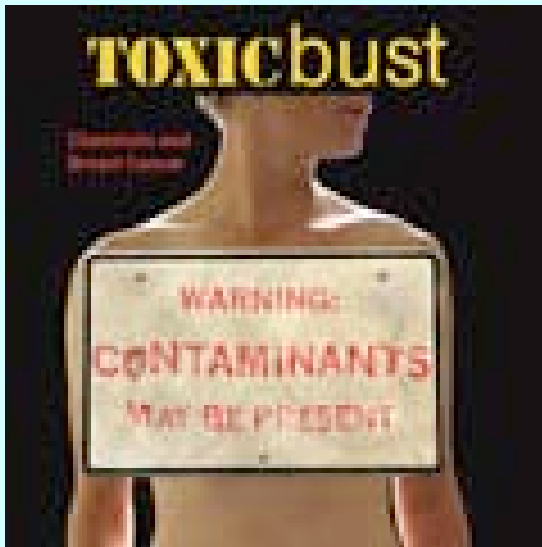


WHO CARES WHERE TOXIC

CHEMICALS END UP?

The world should be the safest place on earth. But today our bodies are contaminated with over 300 man-made chemicals, to which our great-grandparents were never exposed. Many of these pollutants are found in intensively-farmed food or everyday products and some have been linked with birth defects in people and wildlife.

WWF is campaigning for the elimination of these hazardous chemicals, so that the only thing we pass on to our children is our genes. To find out how to help WWF and to reduce your risk, call 01483 426333 or visit www.wwf.org.uk/whocares



Overview

- Definition & History
- Human Biologic Media
- What is a Biomarker?
- Sources of Chemicals Measured
- Reasons for Biomonitoring Programs
- Biomonitoring Considerations
- Limitations of Biomonitoring
- Biomonitoring Cautions
- The Precautionary Principle

Human Biomonitoring

Measurement of specific chemicals in human tissues, providing a picture of the amount actually absorbed and retained within the body

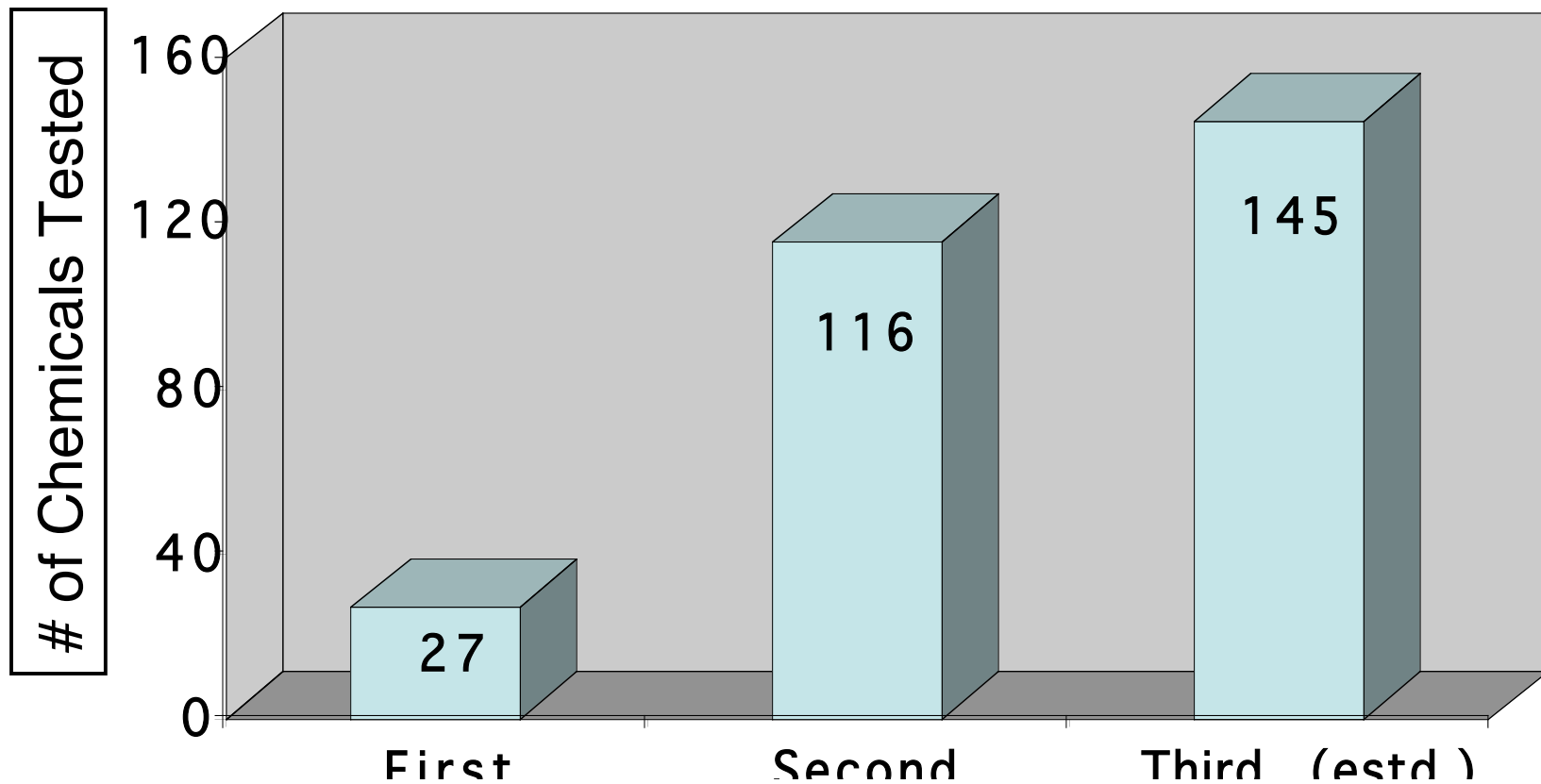


History of Biomonitoring

- General principle applied in late 1800s to monitor treatment of rheumatism with salicylic acid
- Used for decades to measure exposure to chemicals in the workplace setting
- Evolved to assess exposures of general population to industrial chemicals (CDC)
- Part of total program to characterize exposure
 - Can reveal subtle differences in individual susceptibility to particular agents
 - Improved worker safety
 - Aided markedly by “toxicogenomics” (proteomics, metabolomics...)

Biomonitoring by the CDC

National Reports on Human Exposure to Environmental Chemicals



Human Biologic Media in Biomonitoring

- Whole blood / serum
- Urine
- Adipose tissue (fat)
- Hair
- Breast milk
- Saliva / sputum
- Semen

Human Biologic Media in Biomonitoring

- Whole blood / serum
 - Most common sample collected
 - Regularly replenished
 - Common pathway for most chemicals and their metabolites
 - Blood lipids can be evaluated to measure many fat-soluble chemicals
 - Some people opposed to blood draws
 - With short half life of RBC, past exposures can be underestimated

Human Biologic Media in Biomonitoring

- Urine
 - Noninvasive
 - Few parent compounds excreted unchanged in urine, so metabolites often tracked instead
 - For chemicals slowly metabolized, frequently need 24 hour urine
 - Requires diligence on part of subject, possible sample integrity issues

Human Biologic Media in Biomonitoring

- Adipose tissue (fat)
 - Fat biopsies used to measure fat-soluble chemicals
 - Useful for dioxins, furans, PCBs, flame retardants
 - Lab techniques on blood lipid fractions markedly improved since 1990
 - Very few fat biopsies now collected

Human Biologic Media in Biomonitoring

- Hair
 - Useful for exposure to certain metals (methylmercury, arsenic)
 - Region of hair sampled can create big difference in results of testing
 - Shampoos/conditioners confound by removal and/or addition of compounds
 - Few studies to compare environmental exposure levels to measured hair values
 - Chiefly employed as screening tool

Human Biologic Media in Biomonitoring

- Breast milk
 - Most fat-soluble chemicals concentrated in breast milk
 - Samples relatively easy to collect
 - Impact should be greatest on breastfeeding infant, but few reports issued to demonstrate this
 - Many state government proposals to assess background levels of chemicals in breast milk

Human Biologic Media in Biomonitoring

- Saliva / sputum
 - Saliva produced by salivary and mucous glands
 - Endogenous steroid hormone levels
 - Not widely used today, but holds promise for future noninvasive method
 - Sputum has highly variable sample quality
 - Invasive procedures minimize this problem
 - Used to monitor for asbestos bodies
 - Utility may improve in future, but current use highly selective

Human Biologic Media in Biomonitoring

- Semen
 - Evaluated in sperm banks to assess sample composition and to minimize contamination of specimens
 - Access to samples more complicated
 - Some researchers feel that this fluid holds great potential for future studies

What is a Biomarker?

a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathologic processes

(www.fda.gov, 2005)

What is a Biomarker?

- **Exposure**
 - Exogenous chemical or its metabolites
- **Effect**
 - Biochemical, physiologic or other alteration in a biologic process
- **Susceptibility**
 - Indicator of an inherent or acquired limitation to responding to a chemical challenge

(National Research Council, 1987)

What is a “Good” Biomarker?

- High sensitivity
- High specificity
- Biologically relevant
- Practically and Economically Feasible

Cost of Measuring Chemicals

- Lead and metals relatively inexpensive
 - \$10 - \$50 per test
- Dioxins and immunologic testing much more expensive
 - Can cost several hundred dollars per test

Starting Biomonitoring Programs

- CDC provided total of \$10M distributed to 33 states in FY 2002 and FY 2003 to perform planning for biomonitoring programs
- Less than \$3M was provided in FY 2004 to actually start implementing these programs in only eight states (NH, NY, “Rocky Mountain Consortium”)

Source: Assoc. Public Health Labs May, 2004

Sources of Chemicals Measured

- **Anthropogenic**
 - Workplace
 - Consumer products
 - Foods
 - Air, water, soil
- **Normal biologic processes**
 - Metabolism of absorbed agents
- **Naturally occurring food chemicals**
- **Environment**
 - Forest fires



Reasons for Biomonitoring Programs

- Discover which chemicals are absorbed by members of society and at what concentrations
- For known toxic chemicals (such as lead), to determine the prevalence of people with levels above recommended limits
- Establish reference ranges for use by physicians and scientists to identify people and groups with unusually high exposures
- Assess effectiveness of public health efforts to reduce exposure to certain chemicals

Reasons for Biomonitoring Programs

- Determine if exposure levels are higher in certain ethnic groups, children, women of childbearing age, senior citizens...
- Track trends in levels of population exposure over time
- Set priorities for research on human health effects for agents of interest

Biomonitoring Considerations

- Measuring “body burden” of chemical provides accurate measure of actual human exposure and physical retention
 - No assumptions needed regarding ingestion or inhalation rate, bioavailability or frequency of exposure
- Can provide specific individual information regarding his or her unique set of exposures
- Comparison with “background” levels important to determine if excessive exposure has occurred

Biomonitoring Considerations

- Ideally, collect biomonitoring data at same time as environmental exposure data
- If exposure data not available, may need to rely upon mathematical calculations of exposure
 - These will usually require certain assumptions, such as quantity of air breathed, amount of food eaten, behavior of “typical” individual, period of exposure
 - Without confirmation of these estimates through biologic sampling, validity of assumptions cannot be assured

Biomonitoring Considerations

- For persons with multiple sources of possible exposure, often difficult to determine the magnitude of individual contributions to total
- One sample can only reflect a single point in time
 - Pharmacokinetics and metabolism need to be considered
 - One sample reading could represent exposure from yesterday, last week, or thirty years ago
- Detection of a past exposure does not necessarily lead to increased risk

Limitations

- Presence of a biomarker does not reveal source or route of exposure for a given substance
- Our vastly improved abilities to detect have often outstripped our abilities to detect meaning
 - Not enough published data to predict health consequences of elevated biomarker levels
- Many chemicals highly resistant to degradation (PCBs, dioxins)
 - Half lives often measured in years
 - High risk of confounding data
- Many metals, volatile organic compounds and water soluble compounds rapidly eliminated
 - Half lives can be minutes to hours
 - Difficult to obtain consistent suitable samples

Benefits of Biomonitoring

- Provides potentially rich picture of an individual's past exposures
- May identify long-term trends in the population
- Can discover geographic locations where body burdens significantly different from general population
- Gives powerful tool for epidemiologic studies
 - Provides unequivocal evidence of exposure
 - Reduces need for calculated approximations
- Evaluate effectiveness of policy decisions to reduce or eliminate certain compounds in the environmental or occupational setting

Proper Use of Biomonitoring?

Reporting a proven health hazard
vs. alarming the public

- Breast milk situation in California and elsewhere



**MOMs...
and POPs**

Persistent
Organic
Pollutants
in the diets of
pregnant and
nursing women

“We Scare Because We Care”

Table 1. A pregnant or nursing woman eats more than the average man 16 of the 50 most heavily POP-contaminated foods in the U.S.

Most contaminated foods consumed more by pregnant women than men	Persistent Organic Pollutant
american cheese	dieldrin, DDT, heptachlor epoxide, hexachlorobenzene
butter	chlordane, dieldrin, DDT, heptachlor epoxide, hexachlorobenzene
cheddar cheese	dieldrin, DDT, heptachlor epoxide, hexachlorobenzene
cheeseburgers	dieldrin, DDT, heptachlor epoxide
dill pickles	chlordane, dieldrin, DDT, toxaphene, heptachlor epoxide
hamburgers	dieldrin, DDT, heptachlor epoxide, hexachlorobenzene
lasagna with meat	dieldrin, DDT
peanut butter	dieldrin, DDT, toxaphene, hexachlorobenzene
peanuts	dieldrin, DDT, toxaphene, hexachlorobenzene
pepperoni pizza	dieldrin, DDT
potato chips	chlordane, dieldrin, DDT, heptachlor epoxide
pumpkin pie	dieldrin
raisins	DDT
sour cream	dieldrin, DDT, heptachlor epoxide, hexachlorobenzene
vanilla ice cream	dieldrin, DDT
whole milk	dieldrin, DDT

Source: Environmental Working Group. Compiled from Food and Drug Administration Total Diet Study, 1991-1997, and U.S. Department of Agriculture's Continuing Survey of Food Intake by Individuals, 1994-1996.

Reasserting the Benefits

AMERICAN ACADEMY OF PEDIATRICS

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

2005

Section on Breastfeeding

Breastfeeding and the Use of Human Milk

ABSTRACT. Considerable advances have occurred in recent years in the scientific knowledge of the benefits of breastfeeding, the mechanisms underlying these benefits, and in the clinical management of breastfeeding. This policy statement on breastfeeding replaces the 1997 policy statement of the American Academy of Pediatrics and reflects this newer knowledge and the supporting publications. The benefits of breastfeeding for the infant, the mother, and the community are summarized, and recommendations to guide the pediatrician and other health care professionals in assisting mothers in the initiation and maintenance of breastfeeding for healthy term infants and high-risk infants are presented. The policy statement delineates various ways in which pediatricians can promote, protect, and support breastfeeding not only in their individual practices but also in the hospital, medical school, community, and nation. *Pediatrics* 2005;115:496–506; *breast, breastfeeding, breast milk, human milk, lactation.*

tions are consistent with the goals and objectives of *Healthy People 2010*,⁴ the Department of Health and Human Services' *HHS Blueprint for Action on Breastfeeding*,⁵ and the United States Breastfeeding Committee's *Breastfeeding in the United States: A National Agenda*.⁶

This statement provides the foundation for issues related to breastfeeding and lactation management for other AAP publications including the *New Mother's Guide to Breastfeeding*⁷ and chapters dealing with breastfeeding in the AAP/American College of Obstetricians and Gynecologists *Guidelines for Perinatal Care*,⁸ the *Pediatric Nutrition Handbook*,⁹ the *Red Book*,¹⁰ and the *Handbook of Pediatric Environmental Health*.¹¹

THE NEED

Child Health Benefits

Human milk is species-specific, and all substitute feeding preparations differ markedly from it, making

ABBREVIATIONS. AAP. American Academy of Pediatrics; WIC.

Throwing out the Breast Milk...

“Breastfeeding provides health, nutritional, immunologic, developmental, psychological, social, economic and environmental advantages unmatched by other feeding options.”

- *American Academy of Pediatrics*

"Breast-feeding reduces the risk of asthma. Breast-feeding reduces the risk of sudden infant death syndrome. Breast-fed children are also less likely to be obese later in life."

- *U.S. Surgeon General David Satcher, M.D., Ph.D.*

Throwing out the Breast Milk...

"When it comes to nutrition, the best first food for babies is breast milk."

- *U.S. Food and Drug Administration*

"The benefits of breast feeding far outweigh potential risks."

- *U.S. Environmental Protection Agency
(Dioxin Reassessment Briefing)*

"Breast feeding should be encouraged and promoted on the basis of convincing evidence of the benefits of human milk to the overall health and development of the infant."

- *World Health Organization*

Precautionary Principle

If the consequences of an action are unknown but are judged to have a high risk, then it is better not to carry out the action rather than risk the chance of a negative outcome.

- Evolved from doctrine of Democratic Socialism in the 1930s
- Favors inaction over freedom to act
- Justifies interventionism in name of protection of citizenry

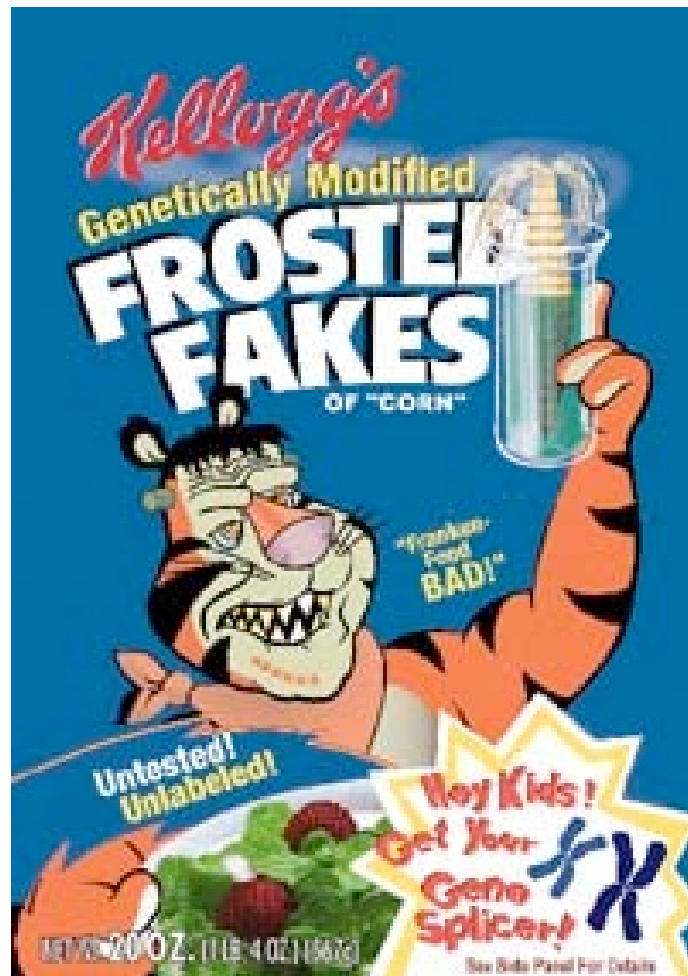
Criticisms of Precautionary Principle

- Every new technology or product carries a risk of negative consequences
- Principle only applied to new technologies - - not the ones that they are designed to replace
- Does not take into account the positive benefits of a product or technology
 - Assumes a zero “lost opportunity cost,” or no cost associated with doing nothing
 - Assumes no cost in actively restricting freedom to operate
 - Malaria example – dangers of spraying insecticides vs. reducing deaths by preventing disease

Where the Precautionary Principle Has Been Applied

- Biologic products (GMO, live vaccines)
- Food safety (Mad cow disease, GM foods, fast-food chili, product tampering)
- Nuclear energy
- Potential for species extinction
- Nanotechnology
- Pharmaceuticals
- Medical devices

Precautionary Principle and Our Diet



Anti-science mayhem: Now fun for the whole family!

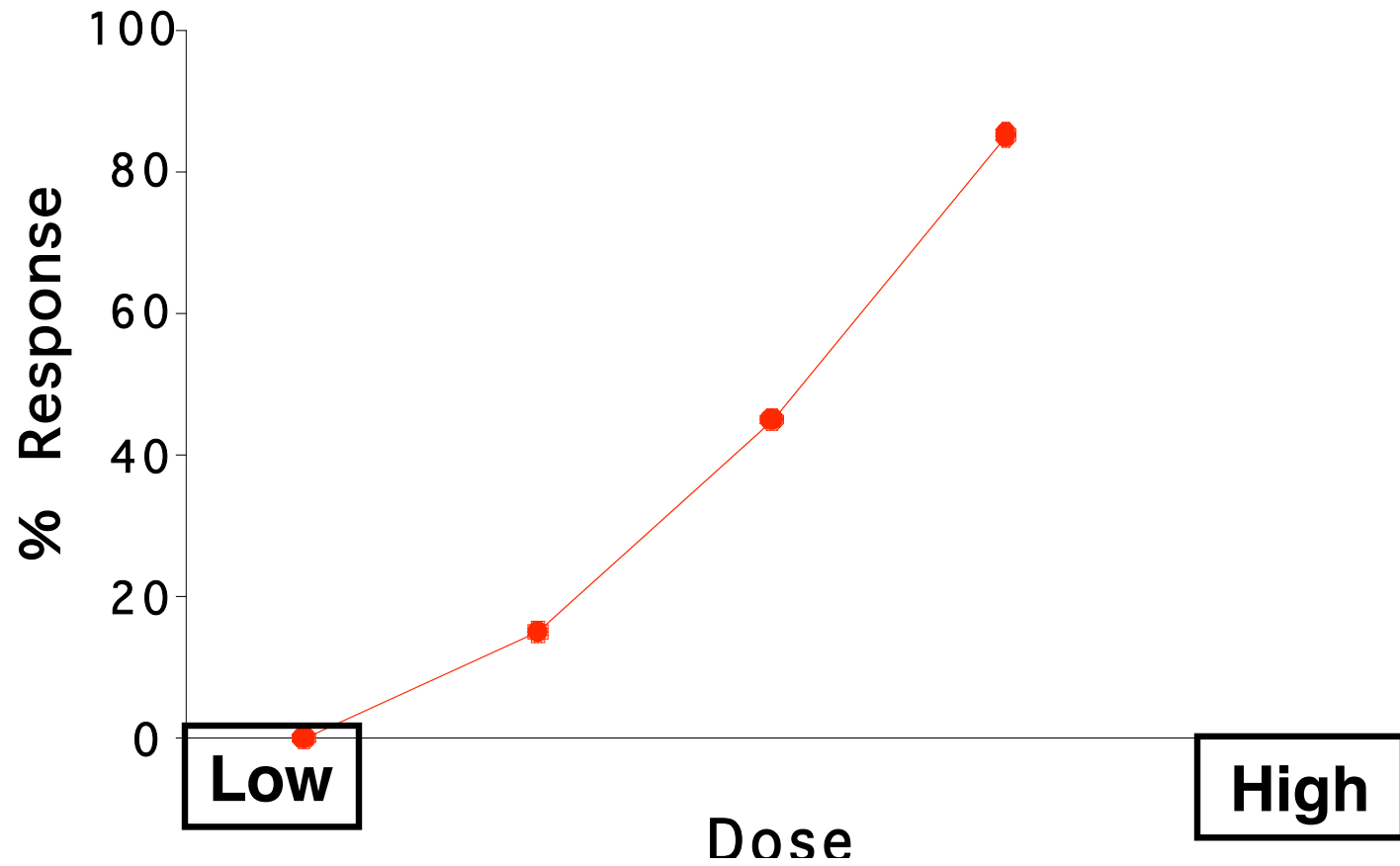
“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.”

- Paracelsus, 1514

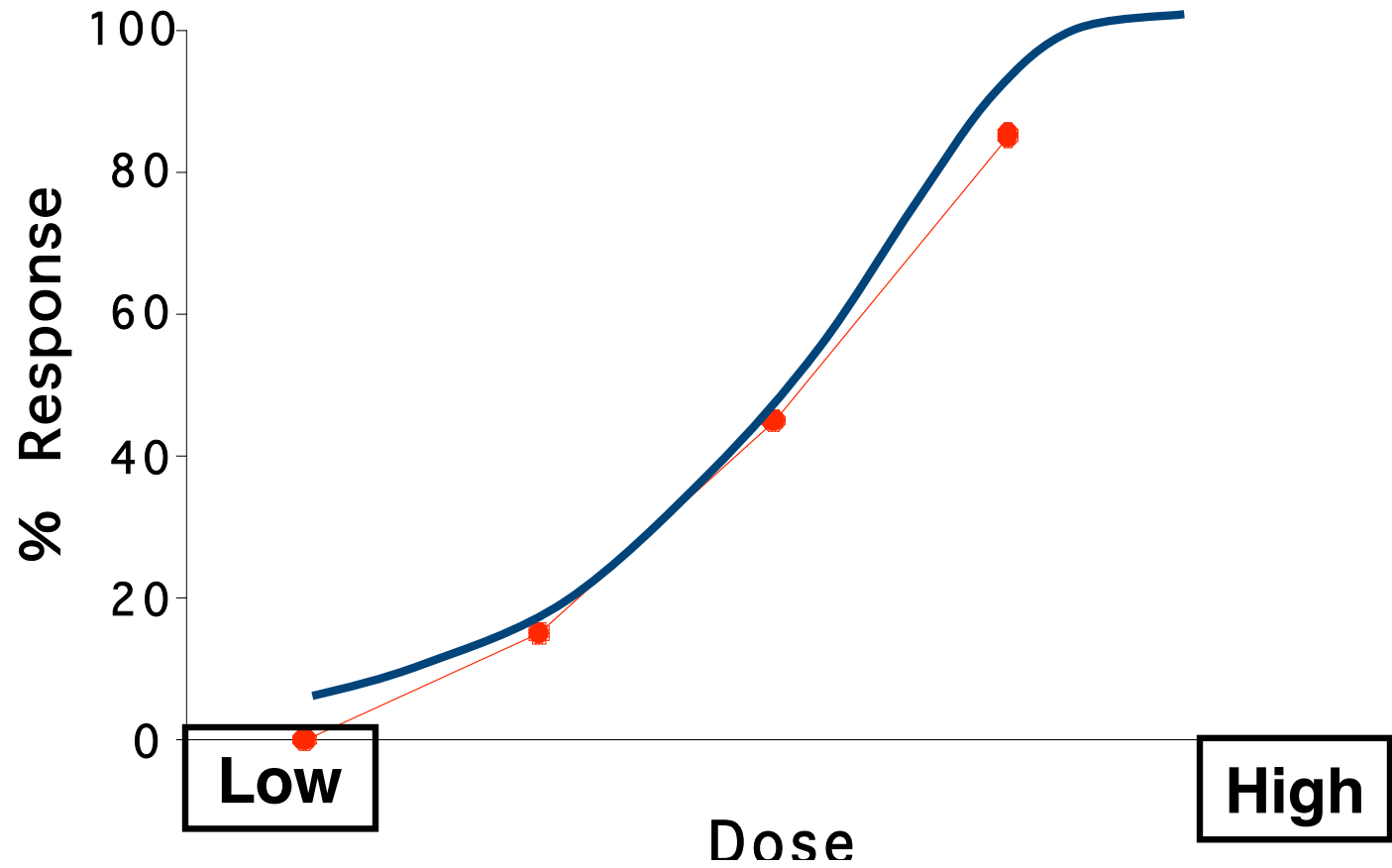


The results of
Risk Assessments
dictate the allowable
concentrations of
toxicants

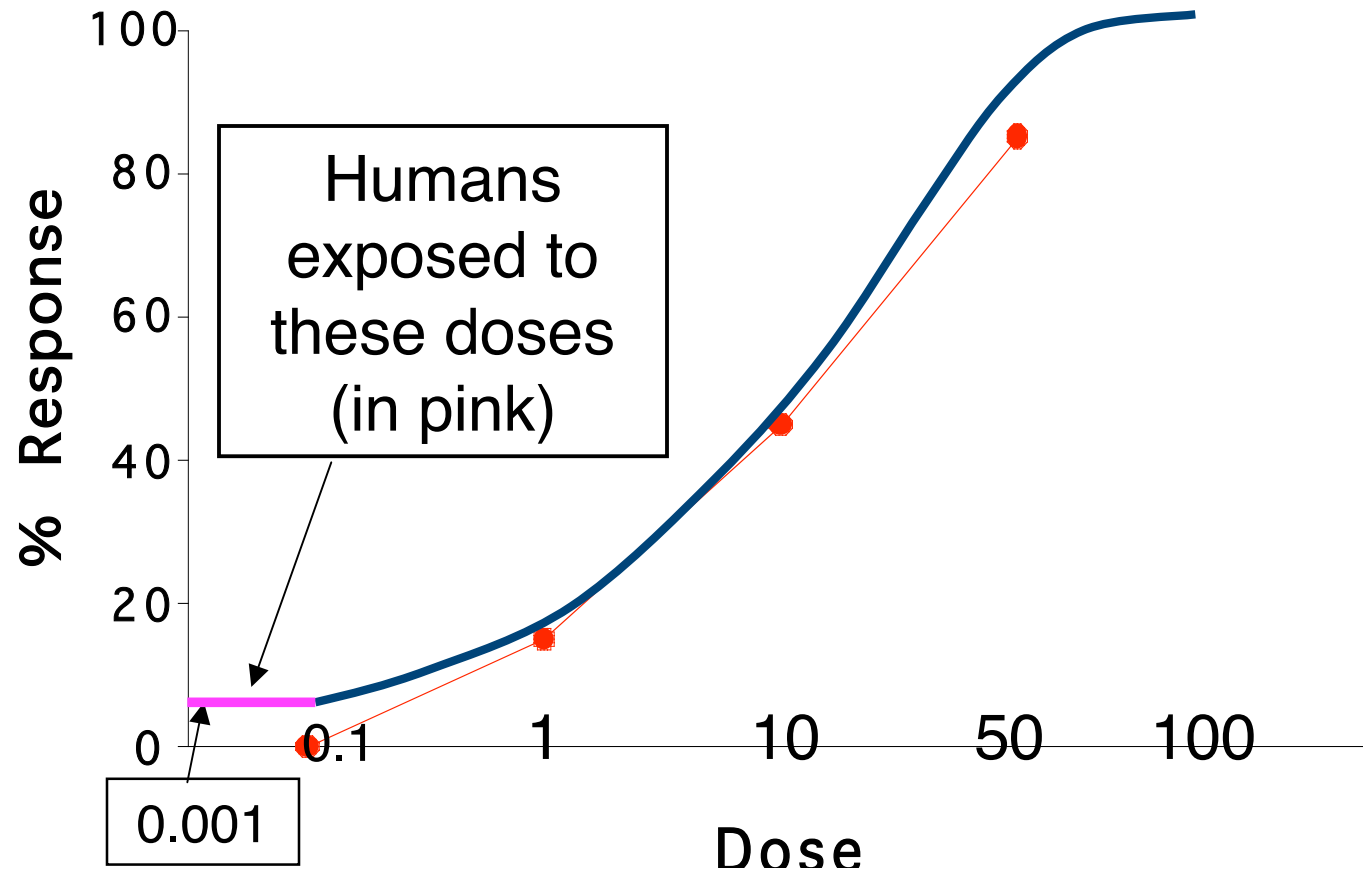
Animal Test Results



Animal Test Results



The Quandary



In the News

State Senate battles hidden chemical risks *Wednesday, June 1, 2005*

As part of a final-week push to move its own legislation by a Friday deadline, the Senate passed Senate Bill 600 by Sen. Deborah Ortiz, D-Sacramento, which would create a state biomonitoring program to catalog chemicals found in human bodies by taking samples of urine, breast milk and blood from volunteers.

Ortiz and other supporters hope to pinpoint chemicals found in the environment and household products that could cause health problems.

"The goal is to be able to detect the level of exposures of various pollutants in Californians' bodies," Ortiz said.

Industry groups opposed to SB 600 argued that it will produce data showing trace chemicals in humans without scientific evidence proving how those chemicals lead to health problems.

"This is taking sheer raw biomonitoring data and jumping to conclusions without going through a real risk assessment," said Tim Shestek, who represents the American Chemistry Council. "This could lead to hysteria when some folks are told that some people in their community have an elevated level of 'chemical X' if you throw that out there without any of the caveats of what that might mean."

- Kevin Yamamura – Sacramento Bee Capitol Bureau

California Senate Bill 600

- Creates statewide biomonitoring program to measure “chemical contaminants” in humans
- Establishes 16 person uncompensated advisory panel, all political appointees
 - 8 persons with scientific backgrounds
 - 8 persons representing “communities of concern”
- Creates educational materials
- Training for scientists and other health professionals

Closing Thoughts

- Biomonitoring is a powerful tool
- Results of biomonitoring studies should be carefully communicated to the public to impart a balanced understanding of their implications
- Legislation and policies enacted must assess the “total societal cost,” weighing the risks and benefits of these actions
- Costs of biomonitoring are a fraction of the total costs involved in linking exposure levels to a measurable health hazard
 - Who will bear these costs?
- Science should rule the day, not emotion



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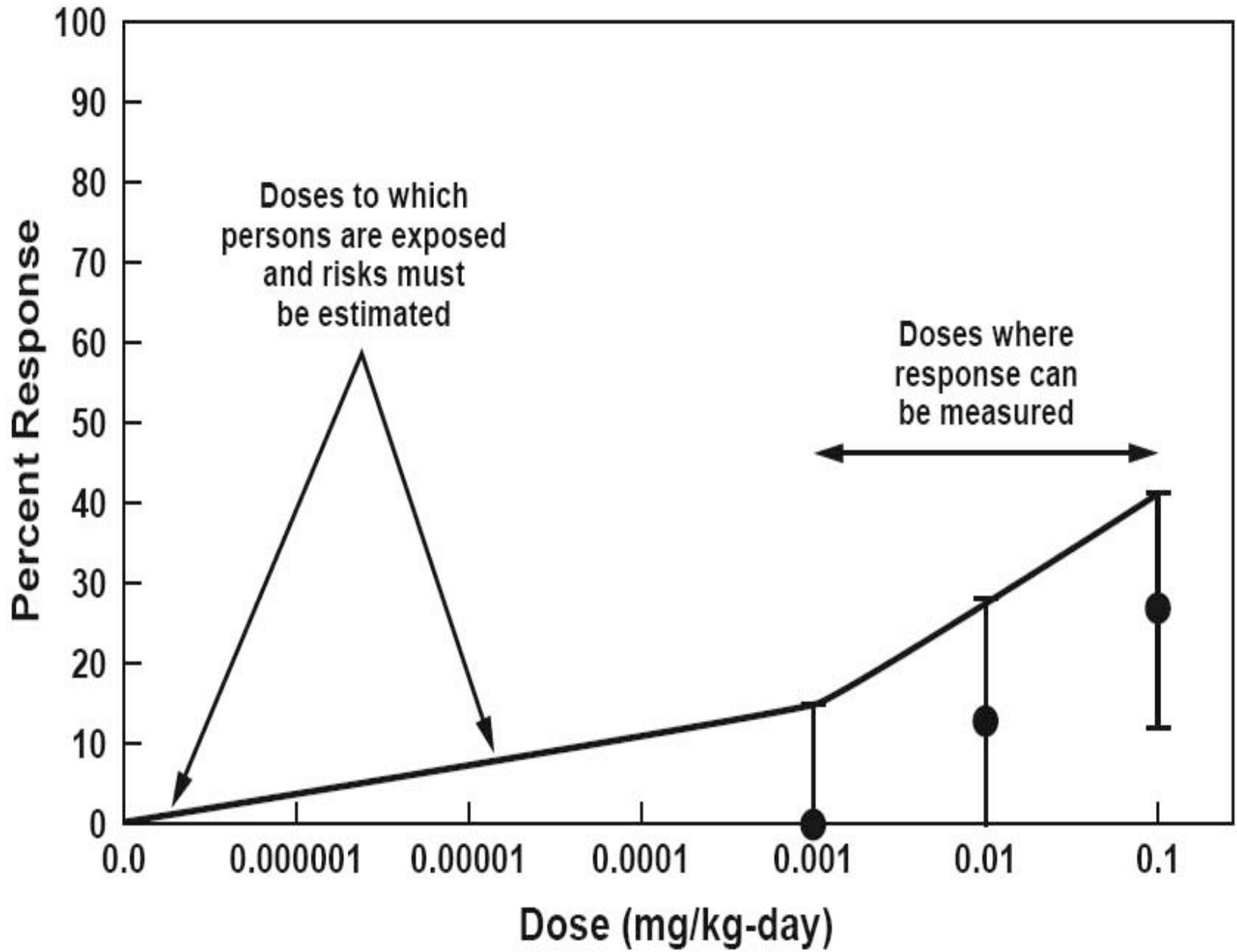
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Appendix







Evolution of Risk Assessment



- Industrial hygienists, toxicologists and occupational physicians have historically placed complete confidence in the dose-response curve
- All chemicals were thought to have a “safe dose”
- From 1940-75, risk assessment sought to establish or estimate the “safe dose” and provided hygienists with a level to guide human exposure

1970's and Early 1980's... the One-Hit Theory, Low-Dose Models and The Ames Test



- In 1968, Mantel and Bryan published their model that assumed a “single hit” had the ability to produce a tumor
- The Ames test told us that we were awash in industrial carcinogens and these were the probable cause of the “cancer epidemic”

During the 1980's...

- Red Book released (1983)
- Regulatory agencies had confidence in the predictive power of the LMS model
- Around 1984, Ames et al told us, “the carcinogenic risk due to the diet is greater than that of industrial chemicals...”



The Mid-1990's...

- Nearly all parties agreed that mechanism of action was more important than once appreciated
- Agencies began to focus on the non-carcinogens
- Non-genotoxic mechanisms were clearly acknowledged

EPA/630/R-96/009

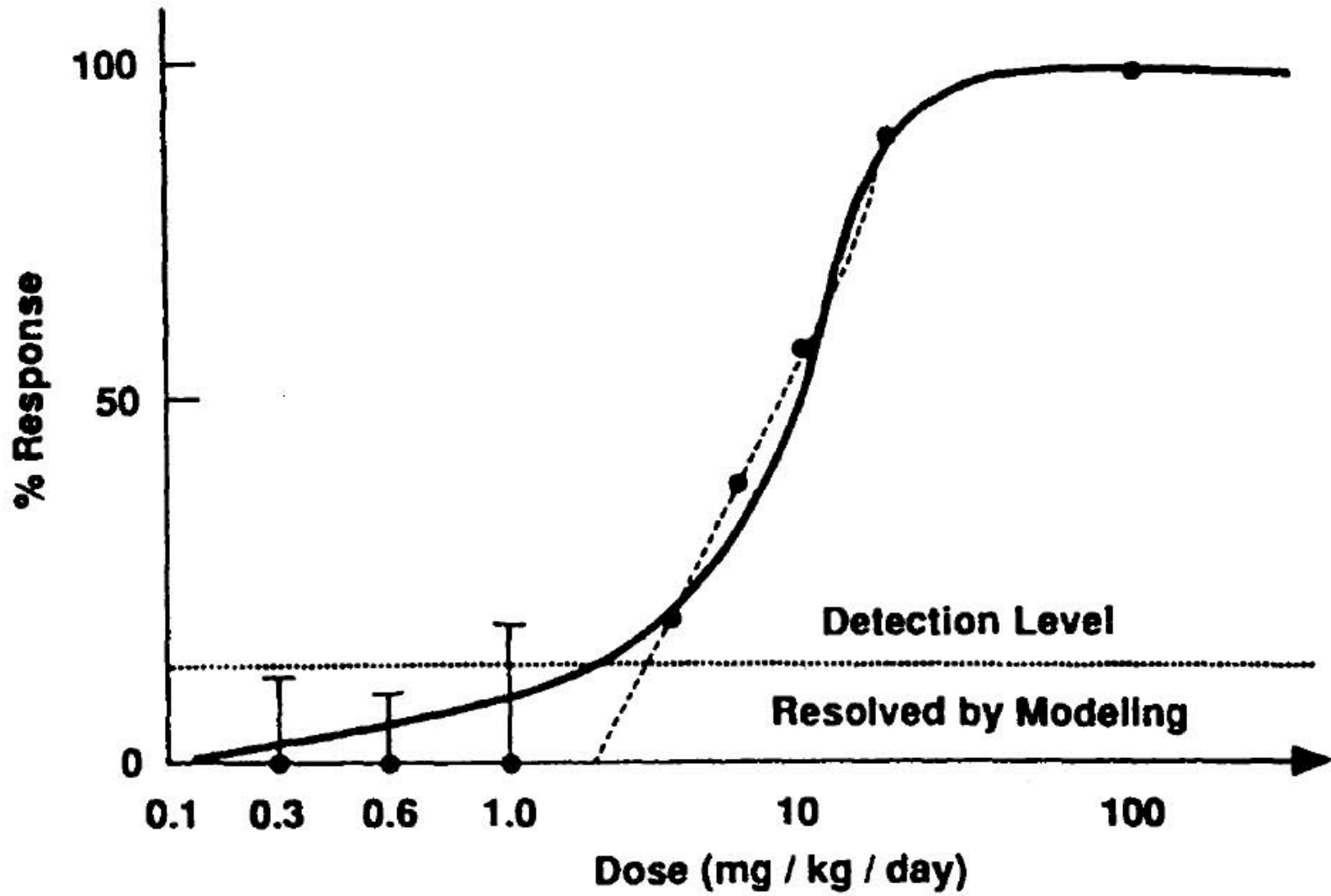
September 1996

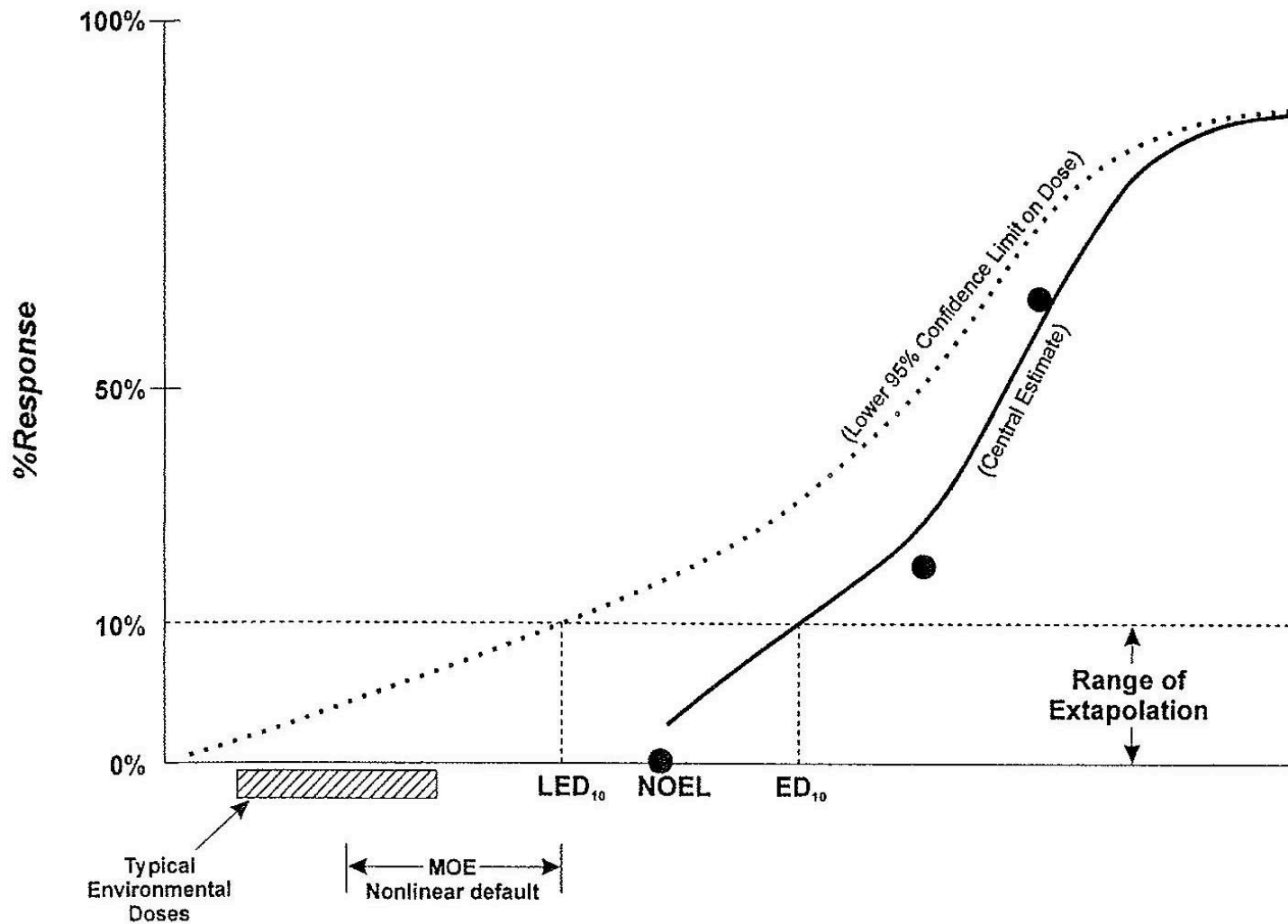
Guidelines for Reproductive Toxicity Risk Assessment

Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

1995 - 2005

A time of no new
regulatory initiatives...





Suggestion #1...

Low dose animal studies that evaluate multiple doses directly below and above the corresponding regulatory standard.



Suggestion #2

Scientists must consider endpoints of regulatory significance.

Cancer	Arsenic Benzene Radionuclides
Kidney Damage	Cadmium Mercury
Liver Damage	Carbon Tetrachloride Dichloroethylene