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Emerging Issues Proposal

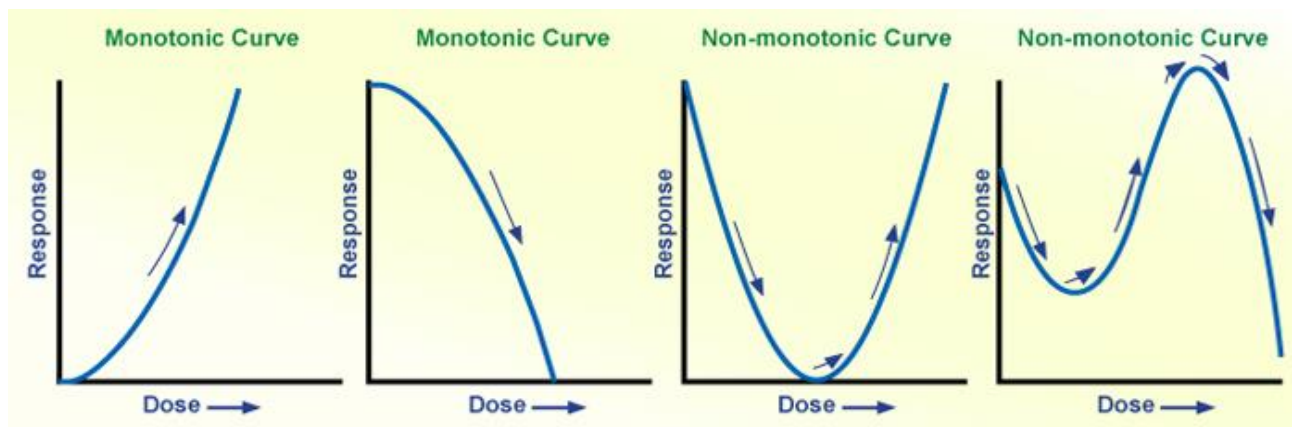
Environmental Chemicals and Low-Dose Non-Monotonic Dose Responses: Is There an Impact on Risk Assessment-Based Study Design and Interpretation?

Sue Yi, Ph.D. (Syngenta Crop Protection, LLC)

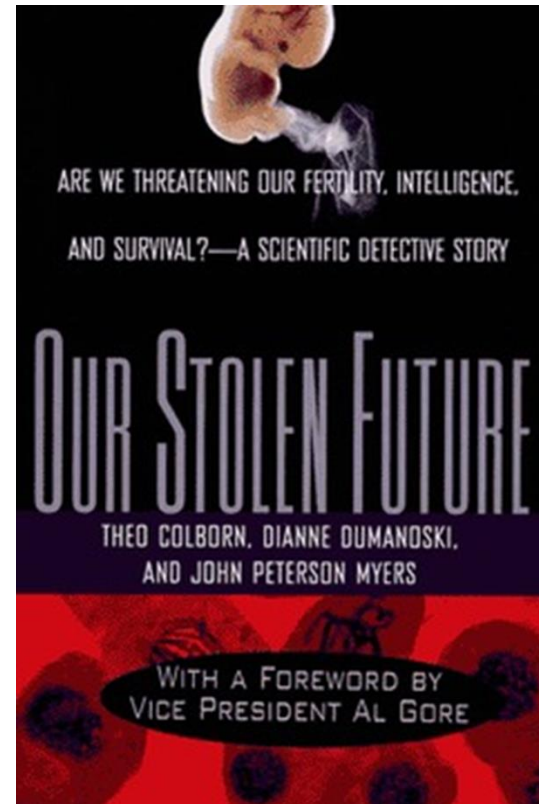
Rita Schoeny, Ph.D. (U.S. Environmental Protection Agency)

Disclaimer

- The views expressed in this presentation are those of the author and do not represent the policy of the U.S. EPA.



EDCs, Low Dose, NMDR, and Controversy



EDCs, Low Dose, NMDR, and Controversy



Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



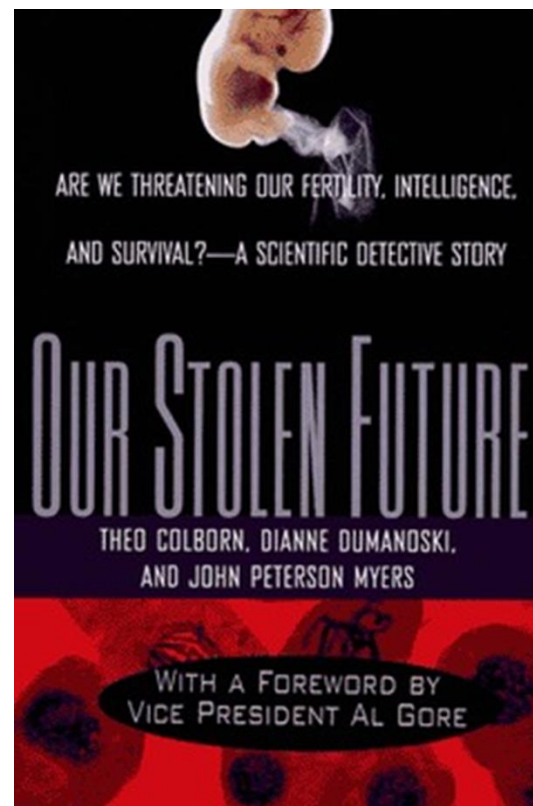
Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel,
David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal,
Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers

Commentary

Low-dose effects and nonmonotonic dose-responses of endocrine disrupting chemicals: Has the case been made?

Lorenz R. Rhomberg*, Julie E. Goodman



EDCs, Low Dose, NMDR, and Controversy

Environmental Chemicals: Evaluating Low-Dose Effects

doi:10.1289/ehp.1205179



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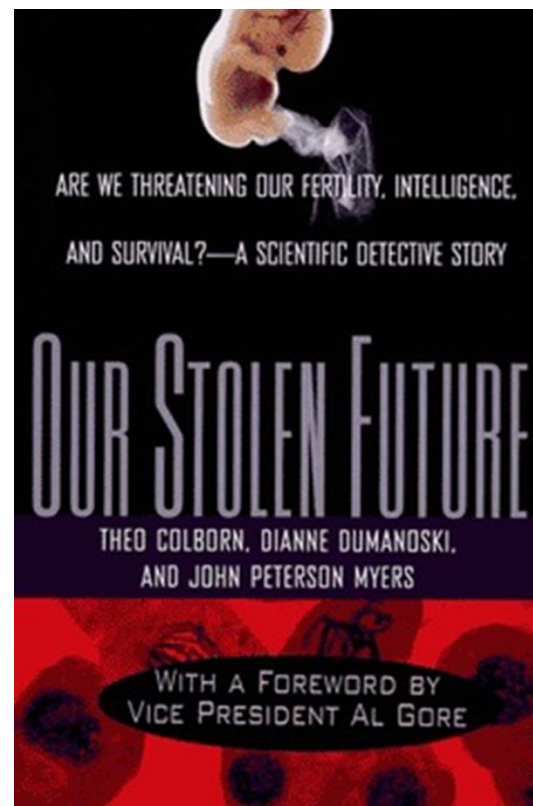
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POSITION STATEMENT

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal



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Editorial

Low dose effects and non-monotonic dose responses for endocrine active chemicals: Science to practice workshop: Workshop summary[☆]



Claire Beausoleil^a, Jean-Nicolas Ormsby^a, Andreas Gies^b, Ulla Hass^c, Jerrold J. Heindel^{d,*}, Marie Louise Holmer^e, Pia Juul Nielsen^e, Sharon Munn^{f,*}, Gilbert Schoenfelder^g

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Endocrine-Disruptor Protection: A State of the Science Report from the Endocrine Society

R. Thomas Zoeller, T. R. Brody, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Centre on Endocrine Disruptors

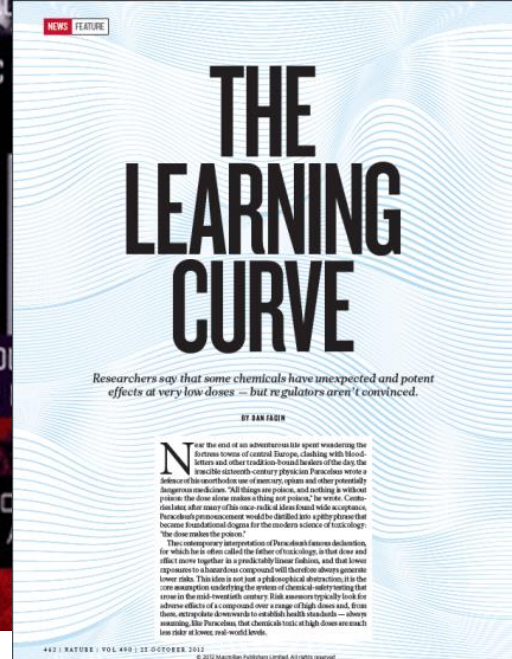
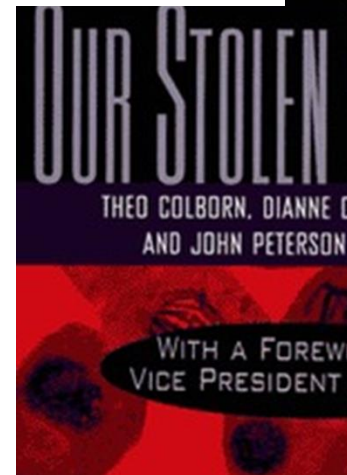
Input for the REACH-review in 2013 on endocrine disruptors (tærskelværdi-projekt, j.nr. MST-621-00050)

Final report 21 March 2013

DANISH CENTRE ON ENDOCRINE DISRUPTERS

Ulla Hass, Sofie Christiansen, Marta Axelstad, Karin Dreisig Sørensen and Julie Boberg

Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark



Researchers say that some chemicals have unexpected and potent effects at very low doses – but regulators aren't convinced.

BY DAN FADEN

Near the end of an advertisement for a new medicine, the authors of a recent issue of *Environmental Health Perspectives* (EHP) warn that the benefits and risks of new drugs may be more complex than we think. The authors, who are leading scientists in the field of toxicology, argue that the current paradigm of testing for safety and efficacy of new drugs is flawed. They argue that the current paradigm of testing for safety and efficacy of new drugs is flawed. They argue that the current paradigm of testing for safety and efficacy of new drugs is flawed.

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Toxicology Letters 223 (2013) A1–A4

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Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Ji David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Wade V. Welshons, R. Thomas Zoeller, and John Petersen

Editorial

Low dose effects of endocrine-disrupting chemicals:

Claire Beausol Holmer^a, Pia J

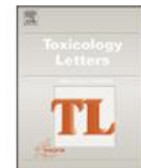
^aFrench Agency for Food Safety and Environmental Health
^bNational Food Institute
^cNational Institute of Environmental Health Sciences
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Editorial

Scientificallly unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles

Endocrine-Disrupting Chemicals: Protection: A State of the Science Report of the Endocrine Society

R. Thomas Zoeller, T. R. Brody, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Centre on Endocrine-Disrupting Chemicals

Input for the

(tærskelværdier)



Lehman-McKeeman, Lois; Society of Toxicology, Kaminski, Norbert; Society of Toxicology, ; Michigan State University, Center for Integrative Toxicology;

The Hazards of Playing it Safe: Perspectives on How the Society of Toxicology Should Contribute to Discussions on Timely Issues of Human and Environmental Safety

Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark

THE LEARNING CURVE

Researchers say that some chemicals have unexpected and potent effects at very low doses – but regulators aren't convinced.

BY DAN FAGER

Not far from the end of an administrative day spent wandering the corridors of a federal agency, I found a group of scientists, some of them in their 20s and 30s, who were talking about the science of low-dose effects. They were talking about the science of low-dose effects, and they were talking about the science of low-dose effects. They were talking about the science of low-dose effects, and they were talking about the science of low-dose effects. They were talking about the science of low-dose effects, and they were talking about the science of low-dose effects.

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EDCs, Low Dose, NMDR, and Controversy

Environmental Chemicals: Evaluating Low Dose Effects

Policy Decisions on Endocrine Disruptors Should Be Based on Science Across Disciplines: A Response to Dietrich *et al.*

A. C. Gore, J. Balthazart, D. Bikle, D. O. Carpenter, D. Crews, P. Czernichow, E. Diamanti-Kandarakis, R. M. Dores, D. Grattan, P. R. Hof, A. N. Hollenberg, C. Lange, A. V. Lee, J. E. Levine, R. P. Millar, R. J. Nelson, M. Porta, M. Poth, D. M. Power, G. S. Prins, E. C. Ridgway, E. F. Rissman, J. A. Romijn, P. E. Sawchenko, P. D. Sly, O. Söder, H. S. Taylor, M. Tena-Sempere, H. Vaudry, K. Wallen, Z. Wang, L. Wartofsky, and C. S. Watson

Low dose of chemicals:

Claire Beausol Holmer^e, Pia J

^aFrench Agency for Food Safety
^bThe Federal Environment Agency
^cNational Food Institute
^dNational Institute of Environmental Health
^eDanish Ministry of the Environment
^fEuropean Commission
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Centre on Endocrine Disruptors

Input for the

Editorial: An International Riposte to Naysayers of Endocrine-Disrupting Chemicals

Andrea C. Gore, PhD

Editor-in-Chief, *Endocrinology*, Gustavus and Louise Pfeiffer Professor of Pharmacology and Toxicology, The University of Texas at Austin, Austin, Texas 78712

Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark



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Bergman *et al.* *Environmental Health* 2013, 12:69
<http://www.ehjournal.net/content/12/1/69>



ENVIRONMENTAL HEALTH

COMMENTARY

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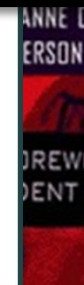
Science and policy on endocrine disruptors must not be mixed: a reply to a “common sense” intervention by toxicology journal editors

Åke Bergman^{1*}, Anna-Maria Andersson², Georg Becher³, Martin van den Berg⁴, Bruce Blumberg⁵, Poul Bjerregaard⁶, Carl-Gustaf Bornehag⁷, Riina Bornman⁸, Ingvar Brandt⁹, Jayne V Brian¹⁰, Stephanie C Casey⁵, Paul A Fowler¹¹, Heloise Frouin¹², Linda C Giudice¹³, Taisien Iguchi¹⁴, Ulla Hass¹⁵, Susan Jobling¹⁶, Anders Juul¹⁷, Karen A Kidd¹⁶, Andreas Kortenkamp¹⁰, Monica Lind⁹, Olwenn V Martin¹⁰, Derek Muir¹⁷, Roseline Ochieng¹⁸, Nicolas Olea¹⁹, Leif Norrgren²⁰, Erik Ropstad²¹, Peter S Ross¹², Christina Rudén²², Martin Scheringer²³, Niels Erik Skakkebaek², Olle Söder²⁴, Carlos Sonnenschein²⁵, Ana Soto²⁵, Shanna Swan²⁶, Jorma Toppari²⁷, Charles R Tyler²⁸, Laura N Vandenberg²⁹, Anne Marie Vinggaard¹⁵, Karin Wiberg²⁰ and R Thomas Zoeller³⁰



Toxicological Sciences

Discussions on How the... to Discussions on Environmental Safety



Researchers say that some chemicals have unexpected and potent effects at very low doses – but regulators aren't convinced.

BY DAN FAGER

Not that long ago, an administrator for a major chemical company was asked to consider the possibility of testing for the effects of chemicals at very low doses. The administrator's response was to dismiss the idea as “common sense.” The administrator's response was to dismiss the idea as “common sense.” The administrator's response was to dismiss the idea as “common sense.”

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The Emerging Battlefield: Should the Use of a Nonmonotonic, Non-Threshold Dose-Response Curve for Alleged Endocrine-Disrupting Chemicals Survive a *Daubert/Frye* Challenge?

By Mark C. Surprenant and Diana Cole Surprenant

Mark C. Surprenant is a Partner in the New Orleans office of Adams and Reese LLP. He serves as Practice Team Leader of the agricultural chemicals team and as Liaison Partner of the



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Andrea C. Gore, PhD

Editor-in-Chief, *Endocrinology*, Gustavus and Louise Pfeiffer Professor of Pharmacology and Toxicology, The University of Texas at Austin, Austin, Texas 78712

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Commentary



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ENVIRONMENTAL HEALTH
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Endocrine Disruptors must make sense”
editors
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Jens Juul⁷, Karen A Kidd¹⁶,
Chieng¹⁸, Nicolas Olea¹⁹,
Niels Erik Skakkebaek²,
Charles R Tyler²⁸,
Miller³⁰

Some chemicals have unexpected and potent effects at low doses – but regulators aren't convinced.
BY DAN FADIN
As the end of an administrative year spent wondering the future of endocrine disruptors, clanking with momentum and other traditions toward the end of the day the twentieth-century physician Paracelsus wrote a cautionary note of necessity: optimum and other potentially deleterious. “All things are poisons, and nothing is without dose alone making it so,” he wrote. Centuries later, after many of his successors had been occupied, Paracelsus’ prescription would be classified as a prophetic statement: “The dose makes the poison.”
This interplay of prescription and Paracelsus’ definition, for which he is often called the father of toxicology, in that dose and effect move together as a practically linear continuum, and that lower responses to a hazardous compound will therefore always generate lower risks. This idea is not just a philosophical abstraction, it is the core message underlying the system of chemical safety testing that arose in the mid-twentieth century. Risk assessment typically looks for adverse effects of a compound over a range of high doses and, from there, extrapolates downwards to establish health risk levels – always assuming, like Paracelsus, that chemicals toxic at high doses are much less risky at lower, real-world levels.

EDCs, Low Dose, NMDR, and Controversy

Environmental Chem
Low Dose Effects

Policy Decisions o
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Dietrich et al.

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E. Diamanti-Kandara
C. Lange, A. V. Lee
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P. E. Sawchenko, P.
K. Wallen, Z. Wang

State of the Science Evaluation:

*Nonmonotonic Dose Responses as They Apply
to Estrogen, Androgen, and Thyroid Pathways
and EPA Testing and Assessment Procedures*

DRAFT

U.S. Environmental Protection Agency

Jointly developed by:
Office of Research and Development
Office of Science Policy
National Health and Environmental Effects Research Laboratory
National Center for Environmental Assessment
National Center for Computational Toxicology
Office of Chemical Safety and Pollution Prevention
Office of Pesticide Programs
Office of Pollution Prevention and Toxics
Office of Science Coordination and Policy

June 2013

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Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as They Apply to Endocrine Disruptors

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Friday, May 2, 2014
11:00 a.m. EDT

This prepublication version has been provided to the public to facilitate timely access to the committee's findings. Although the substance of the report is final, editorial changes will be made throughout the text, and citations will be checked prior to publication.

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OF THE NATIONAL ACADEMIES

May 2014

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Endocrine Disruptors must
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... some chemicals have unexpected and potent
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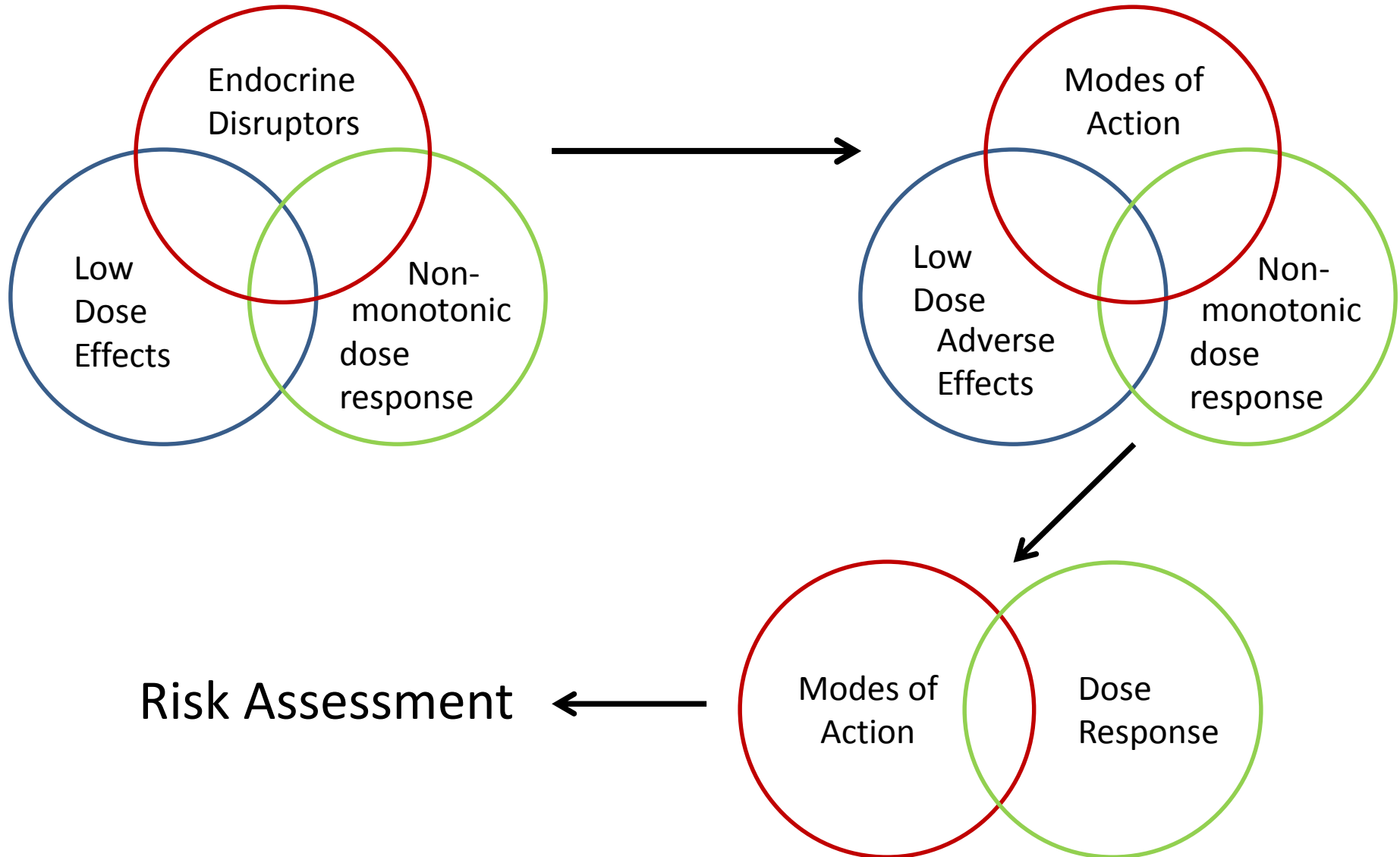
Division of Toxicology and Risk Ass

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Low Dose Effects and NMDR: Beyond The Endocrine System

- The conversation has been focused on endocrine modes of action; however, the notion that low dose/nonmonotonic responses extend to other modes of action is an obvious next step
 - “it is more appropriate to consider lack of thresholds at a population level”
- Therefore, by implication, the conversations and presentations are expanding the issues of low dose effects and non-monotonic dose responses beyond the endocrine system
 - cardiovascular systems
 - neuronal systems

Low Dose Effects and NMDR: Beyond The Endocrine System



What Are the Problems/Issues?

Endocrine Researchers	Toxicologists
Lack of understanding of endocrinology – complex organ system	Lack of understanding of toxicology (endpoint vs. MOA) and pharmacology (potency)
Lack of sensitive endpoints in regulatory toxicity testing – not testing low enough doses	Adverse effects vs. adaptation – (how many animals to test for apical endpoints?)

- Major polarization – speaking very different languages
- Failure to communication among all stakeholders
- Scientific discourse has not always been held
- Opinions need to be science-based and science-directed

What should be addressed?

- Are there fundamental scientific issues regarding non-monotonic dose responses in the “low” dose region that would change the current toxicological testing paradigms?

Objectives

- To provide an environment for open scientific debate/ discussions on nonmonotonic dose responses in the low dose region with the goal to identify key issues.
 - Use current evidence/knowledge on low-dose NMDR theory
- To advance study of the low-dose NMDR issue:
 - Identify the specific research needs
 - Build a framework for evaluation of low-dose NMDR
 - What are requirements for data, statistics, reproducibility, etc.?
 - Develop study designs to address potential low-dose NMDR
 - Develop guidance to ascertain the relevance of low-dose NMDR to risk assessment
- Workshop to garner feedback from other stakeholders; modify the approach if necessary
- Publish papers on the approach and workshop proceedings

Why HESI?

- Provides the neutral forum of scientists (regardless of affiliation) to critically evaluate the issue and develop the most scientifically sound solutions
- Promotes collaborations among different disciplines and sectors
 - Different perspectives
 - Academic
 - Government (Regulatory)
 - Industry
 - Different disciplines
 - Endocrine
 - Toxicology
 - Pharmacology
 - epidemiology
- Organization by a neutral group



U.S. EPA



U.S. FDA

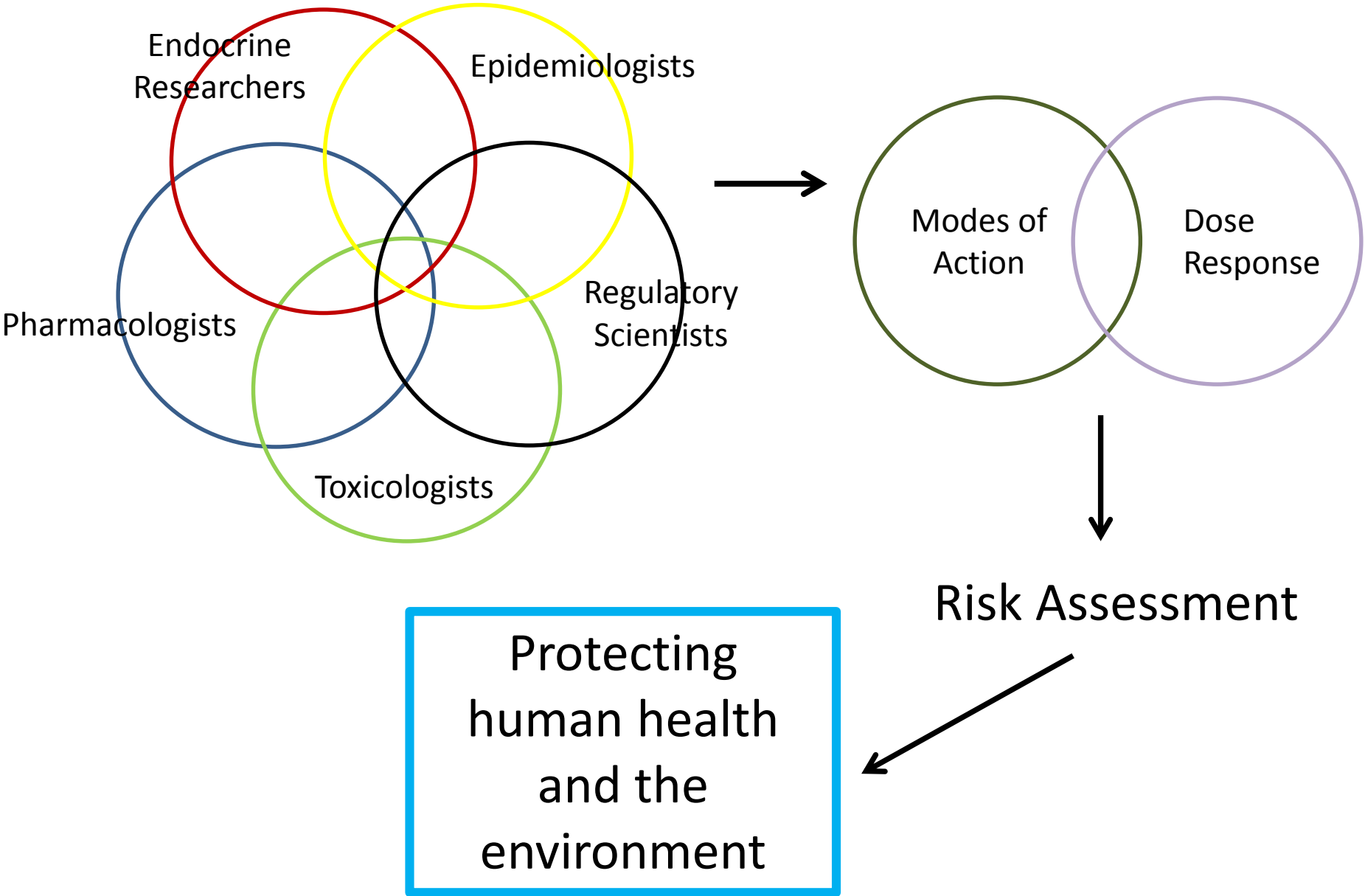
Why HESI?

- This topic has relevance to all sectors involved
- Due to the polarization caused by this topic, this project through HESI has the potential to bridge government, academic, and industry activities
 - To contribute meaningfully to risk assessment and regulation
- Opportunity for HESI to facilitate interdisciplinary approach to define and address relevant issues.

Significance

- Potential to advance the science underlying identification and relevance of nonmonotonic dose responses
 - informing regulatory decisions
 - responding to many of the concerns identified from the National Academies evaluation of the EPA's document on NMDR for endocrine activity
- Outcome of this project will contribute to a consistent and systematic analytic approach to evaluate evidence for NMDR in chemicals with a variety of potential modes of action
- Discussion of
 - specific toxicity-testing strategies that would detect NMDR,
 - Scenarios in which to employ these strategies
 - guidance on identifying adverse and adaptive responses
 - Appropriate statistical considerations, uncertainty analyses
 - Life-stage or susceptibility issues

Significance



Endocrine
Researchers

Epidemiologists

Pharmacologists

Regulatory
Scientists

Toxicologists

Modes of
Action

Dose
Response

Risk Assessment

Protecting
human health
and the
environment