ILSI Health and Environmental Sciences Institute

syngenta

U.S.EPA

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

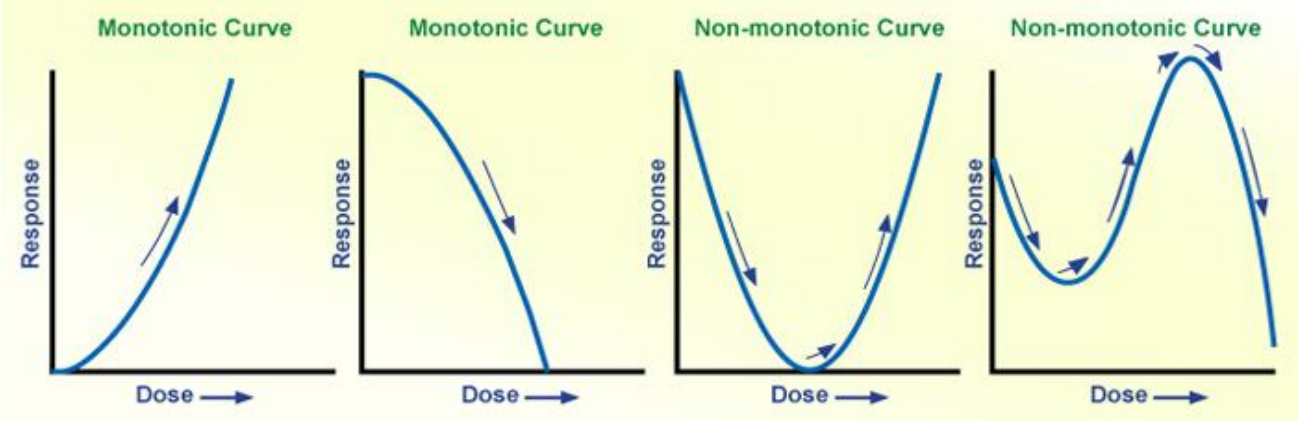
Sue Yi, Ph.D. (Syngenta Crop Protection, LLC)

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

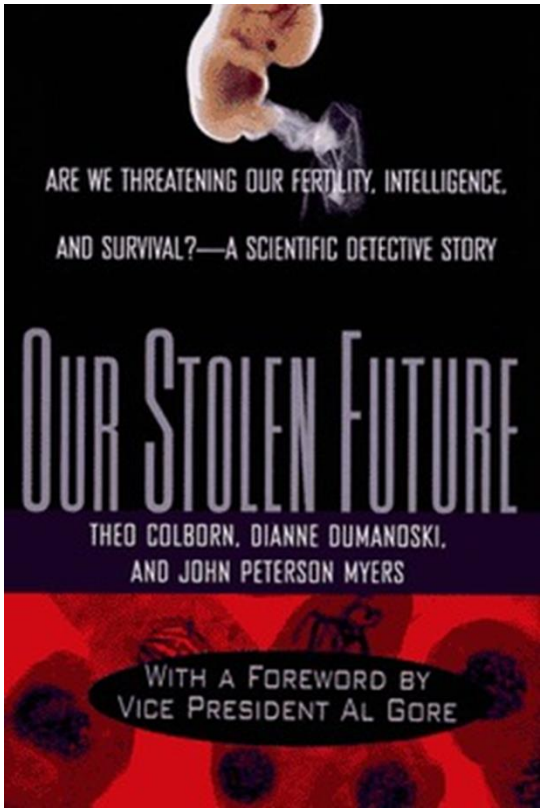
United States Environmental Protection Agency

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

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

Contents lists available at SciVerse ScienceDirect

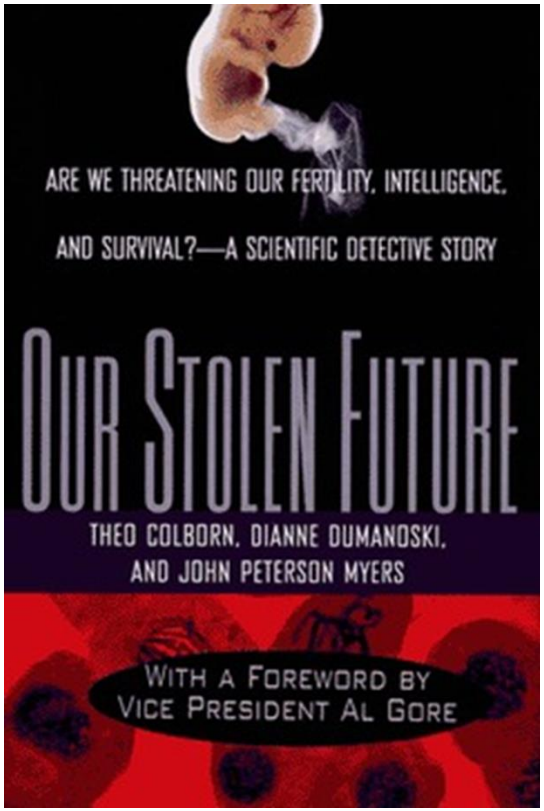
Regulatory Toxicology and Pharmacology

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

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

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

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

Contents lists available at SciVerse ScienceDirect

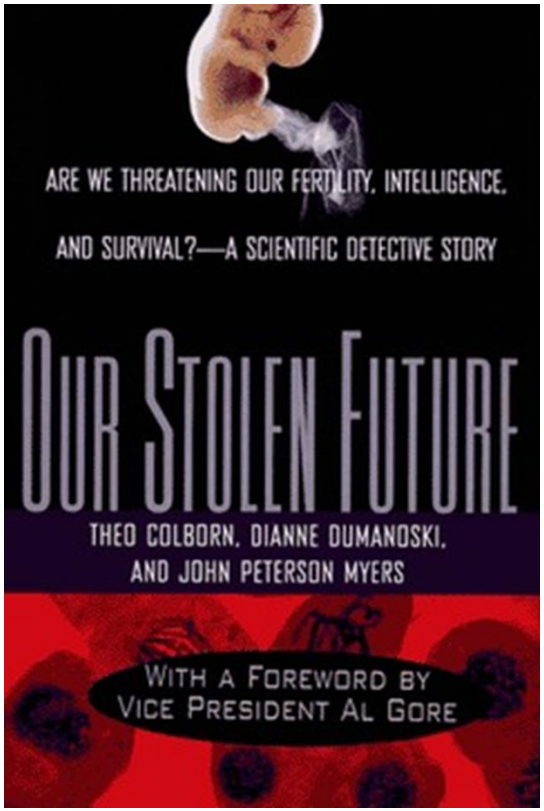
Regulatory Toxicology and Pharmacology

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

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

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

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

Lorenz R. Rhomberg *, Julie E. Goodman

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

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]

[a] French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 27-31 Avenue du Général Leclerc, 94701 Maisons-Alfort Cedex, France
[b] The Federal Environment Agency (UBA), Umweltbundesamt Bismarckplatz 1, 14193 Berlin, Germany
[c] National Food Institute, Technical University of Denmark, Mørkhøj Bygade 19, 2860 Søborg, Denmark
[d] National Institute of Environmental Health Sciences/National Institutes of Health, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709, United States
[e] Danish Ministry of the Environment, Environmental Protection Agency, Strandgade 29, 1401 Copenhagen K, Denmark
[f] European Commission, Joint Research Centre, Via E. Fermi 2749, 21027 Ispra, VA, Italy
[g] Charite Universitatmedizin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany

Endocrine-Disrupti Protection: A State Endocrine Society

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

Centre on Endocrine Disrupters

Input for the REACH-review in 2013 on endocrine disrupters

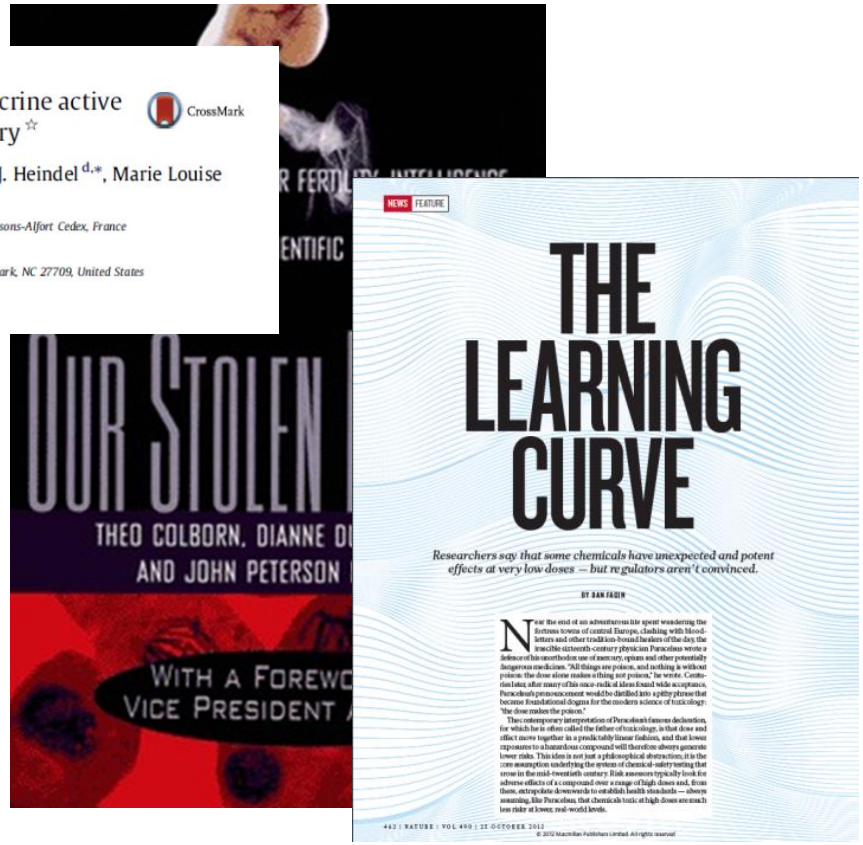
(tærskelværdi-projekt, j.nr. MST-621-00050)

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



EDCs, Low Dose, NMDR, and Controversy

Environmental Chemicals: Evaluating Low-Dose Effects

doi:10.1289/ehp.1205179

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

upting

Hormones and Endocrine-D
Low-Dose Effects and Noni

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

Toxicology Letters 223 (2013) A1–A4

Contents lists available at ScienceDirect

Toxicology Letters

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

Editorial

Low dose el
chemicals:

Claire Beausol
Holmer[e], Pia J

[a] French Agency for Foo
[b] The Federal Environme
[c] National Food Institute
[d] National Institute of E
[e] Danish Ministry of the
[f] European Commission,
[g] Charite Universitatmedizin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany

Editorial

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

Endocrine-Disrupti
Protection: A State
Endocrine Society

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

Centre on Endoc

Input for th

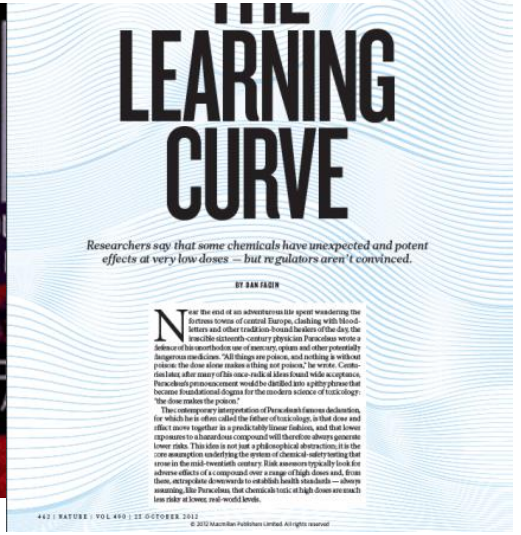
(tærskelv

OXFORD UNIVERSITY PRESS Toxicological Sciences

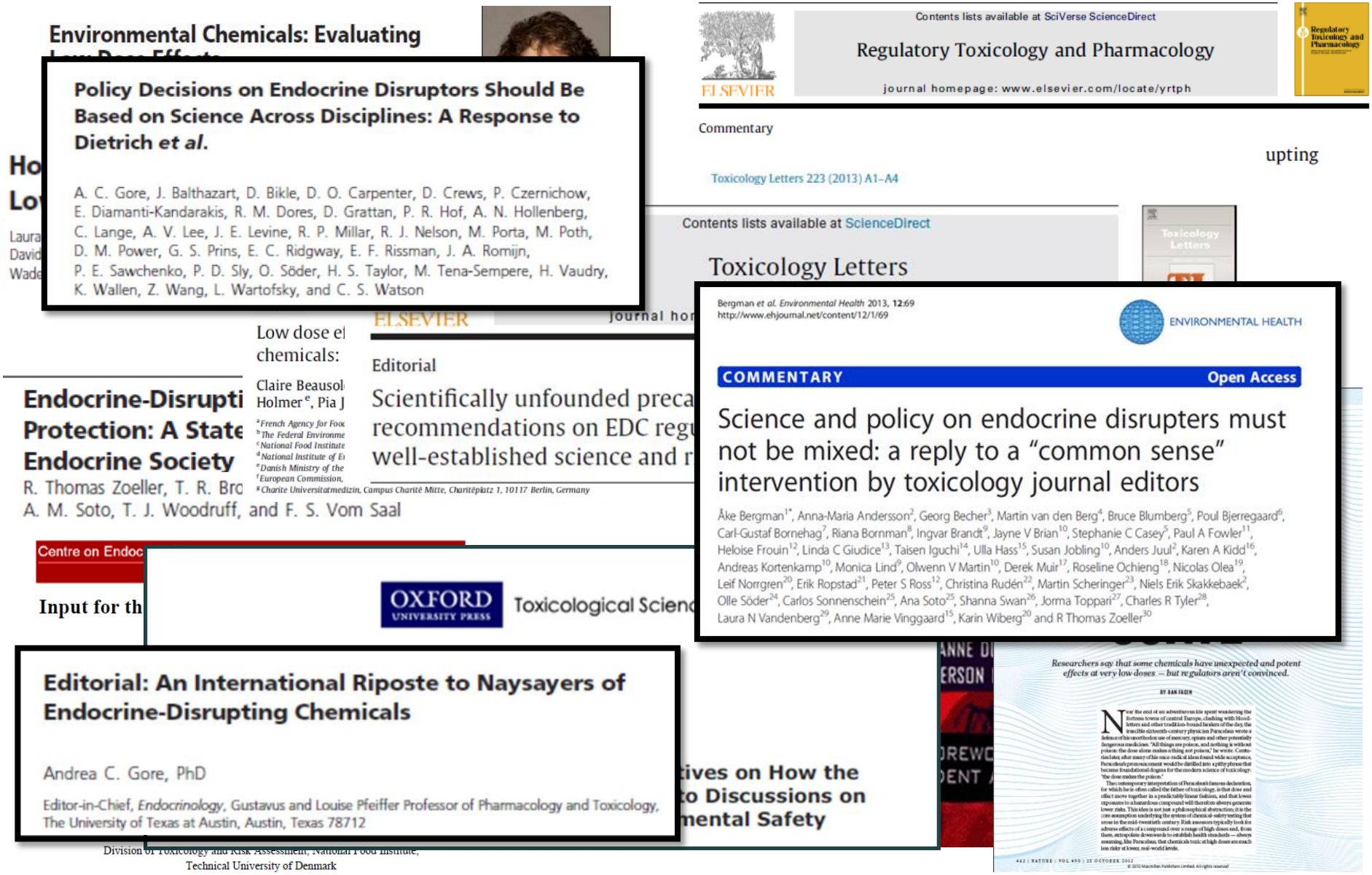
Lehman-McKeeman, Lois; Society of Toxicology,
Kaminski, Norbert; Society of Toxicology, ; Michigan State University,
Center for Integrative Toxicology;

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



EDCs, Low Dose, NMDR, and Controversy



Environmental Chemicals: Evaluating

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

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

upting

Toxicology Letters 223 (2013) A1–A4

Contents lists available at ScienceDirect

Toxicology Letters

Low dose el
chemicals:

Claire Beausol
Holmer[e], Pia J

[a]French Agency for Foo
[b]The Federal Environme
[c]National Food Institute
[d]National Institute of E
[e]Danish Ministry of the
[f]European Commission,
[g]Charite Universitatmedizin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany

Editorial

Scientifically unfounded preca
recommendations on EDC regu
well-established science and r

Endocrine-Disrupti
Protection: A State
Endocrine Society

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

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

ENVIRONMENTAL HEALTH

COMMENTARY Open Access

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

Åke Bergman[1*], Anna-Maria Andersson[2], Georg Becher[3], Martin van den Berg[4], Bruce Blumberg[5], Poul Bjerregaard[6], Carl-Gustaf Bornehag[7], Riana Bornman[8], Ingvar Brandt[9], Jayne V Brian[10], Stephanie C Casey[5], Paul A Fowler[11], Heloise Frouin[12], Linda C Giudice[13], Taisen Iguchi[14], Ulla Hass[15], Susan Jobling[10], Anders Juul[2], Karen A Kidd[16], Andreas Kortenkamp[10], Monica Lind[9], Olwenn V Martin[10], Derek Muir[17], Roseline Ochieng[18], Nicolas Olea[19], Leif Norrgren[20], Erik Ropstad[21], Peter S Ross[12], Christina Rudén[22], Martin Scheringer[23], Niels Erik Skakkebaek[2], Olle Söder[24], Carlos Sonnenschein[25], Ana Soto[25], Shanna Swan[26], Jorma Toppari[27], Charles R Tyler[28], Laura N Vandenberg[29], Anne Marie Vinggaard[15], Karin Wiberg[30] and R Thomas Zoeller[30]

Centre on Endoc

Input for th

OXFORD UNIVERSITY PRESS Toxicological Scienc

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

tives on How the
o Discussions on
mental Safety

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 FAGIN

EDCs, Low Dose, NMDR, and Controversy

Environmental Chemicals: Evaluating

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

A. C. Gore, J. Baltha
E. Diamanti-Kandara
C. Lange, A. V. Lee,
D. M. Power, G. S.
P. E. Sawchenko, P.
K. Wallen, Z. Wang,

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

upting

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

Endocrine-Disru
Protection: A St
Endocrine Socie
R. Thomas Zoeller, T. R
A. M. Soto, T. J. Wood

Centre on Endoc

Input for th

ENVIRONMENTAL HEALTH

Open Access

srupters must
n sense"
editors

e Blumberg[5], Poul Bjerregaard[6],
Casey[5], Paul A Fowler[11],
ders Juul[2], Karen A Kidd[16],
hieng[18], Nicolas Olea[19],
[3], Niels Erik Skakkebaek[2],
Charles R Tyler[28],
ller[30]

Editorial: An I
Endocrine-Dis

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

tives on How the
o Discussions on
mental Safety

some chemicals have unexpected and potent
doses — but regulators aren't convinced.

BY DAN FAGIN

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

EDCs, Low Dose, NMDR, and Controversy

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

Environmental Cher

Policy Decisions c
Based on Science
Dietrich *et al.*

A. C. Gore, J. Baltha
E. Diamanti-Kandara
C. Lange, A. V. Lee,
D. M. Power, G. S.
P. E. Sawchenko, P.
K. Wallen, Z. Wang,

Endocrine-Disru
Protection: A St
Endocrine Socie
R. Thomas Zoeller, T. R
A. M. Soto, T. J. Wood

Centre on Endoc

Input for th

Editorial: An I
Endocrine-Dis

Andrea C. Gore, PhD

Editor-in-Chief, *Endocrinology*, Gu
The University of Texas at Austin,

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

nceDirect

harmacology

/locate/yrtph

Regulatory Toxicology and Pharmacology

upting

Toxicology Letters

ENVIRONMENTAL HEALTH

Open Access

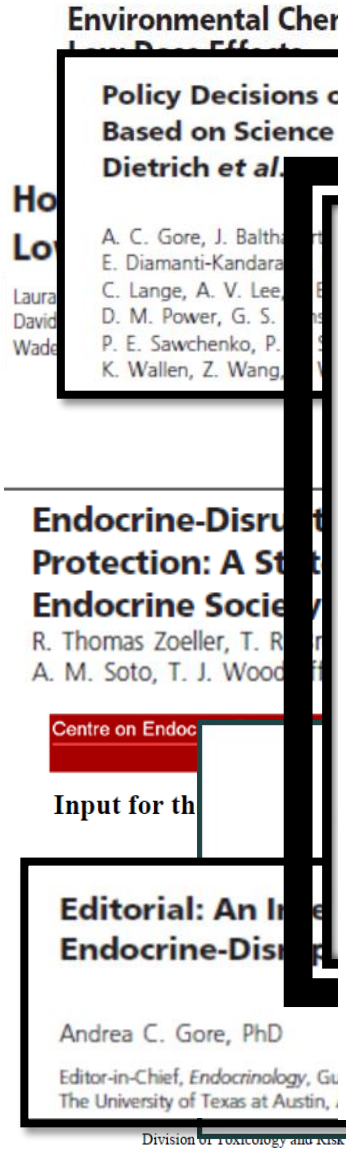
srupters must
n sense"
editors

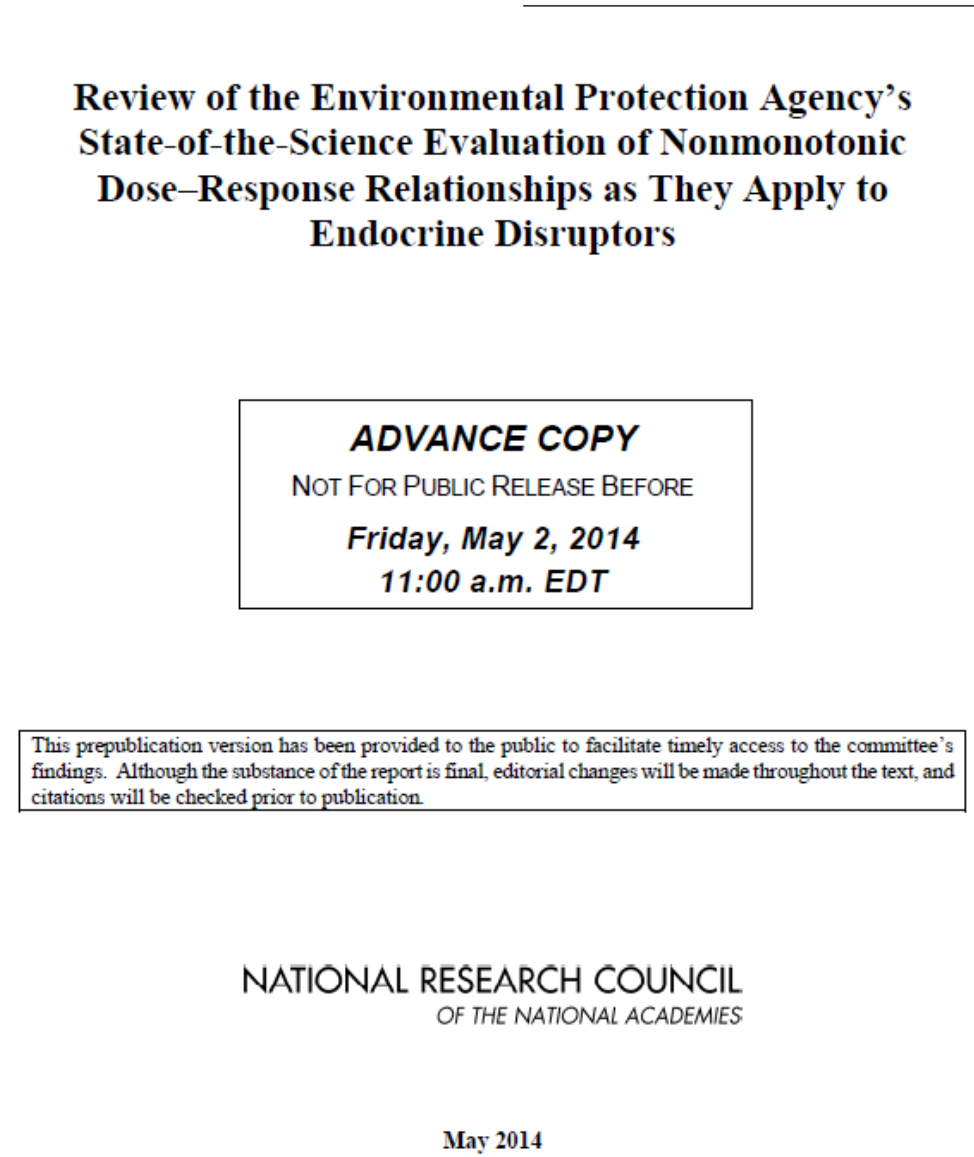
e Blumberg[5], Poul Bjerregaard[6],
Casey[5], Paul A Fowler[11],
ders Juul[2], Karen A Kidd[16],
hieng[18], Nicolas Olea[19],
[3], Niels Erik Skakkebaek[2],
Charles R Tyler[28],
ler[30]

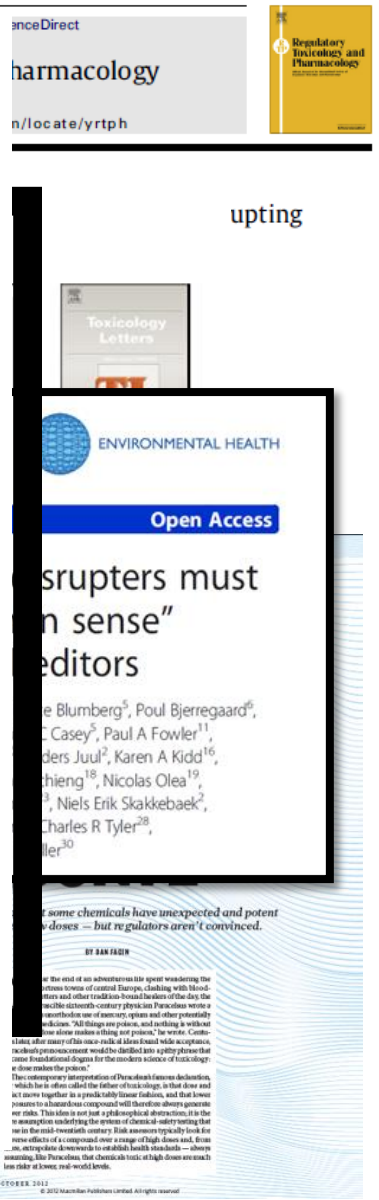
some chemicals have unexpected and potent doses — but regulators aren't convinced.

BY DAN FAGIN

EDCs, Low Dose, NMDR, and Controversy



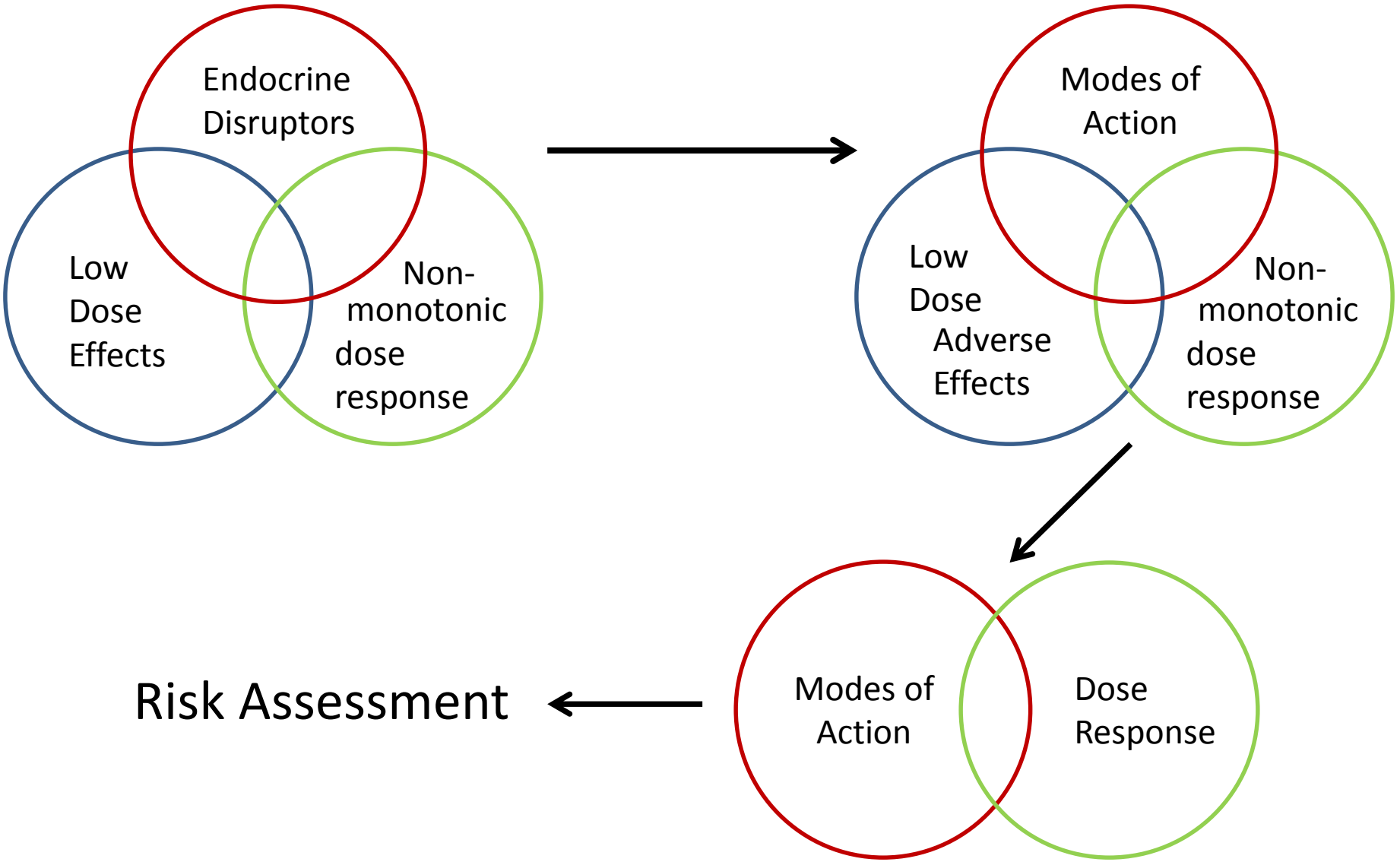




Low Dose Effects and NMDR: Beyond The Endocrine System

- 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

ENDOCRINE SOCIETY

DOW

U.S. EPA

syngenta

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