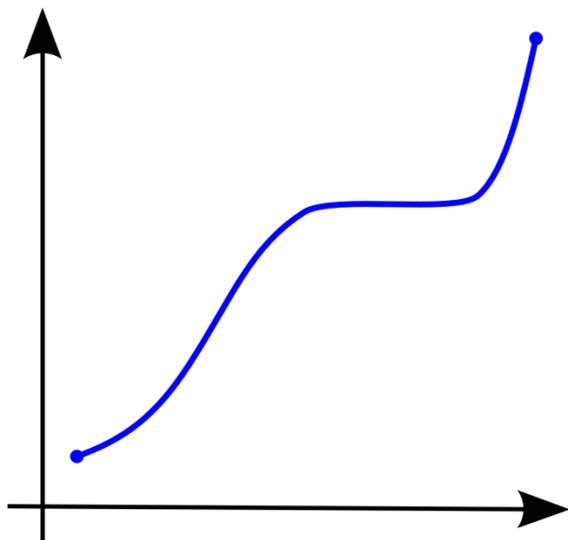


Research Program Integration: Investigating Implications of Non-Monotonic Dose Response Curves (NMDRCs)

Douglas C. Wolf, ORD

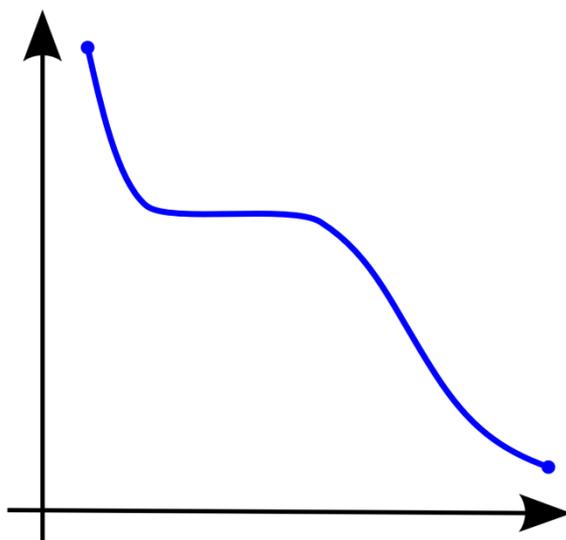


NMDRC – What is it,



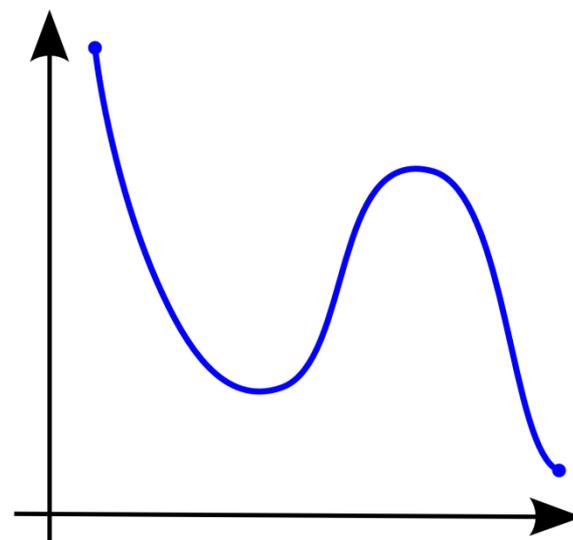
Monotonic increasing

Predictable



Monotonic decreasing

Predictable



Nonmonotonic

Predictable?

and is it important for chemical risk?

Issue: Brief Background

Published Literature:

- Results from epidemiological studies suggest an association between the environmental (or low dose) concentrations of endocrine active chemicals and reproductive and developmental health outcomes
 - These effects have been examined and reported with mixed results in a wide range of animal studies
 - Among the scientific community there is a broad spectrum of interpretation of these findings, in particular as it relates to internal dosimetry

1998 Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)

- Dose selection for studies used in risk assessment must include attention to setting a low dose
- Range-finding studies should include sensitive endpoints that could detect effects at low exposure concentrations

Addressing this Issue: Background

2000 EPA/NIEHS Endocrine Disruptor Low Dose Peer Review Workshop:

www.epa.gov/endo/pubs/edmvs/lowdosepeerfinalrpt.pdf

- **“Low dose”** – a biological change, *not limited to adverse effects*, which occur either at human exposure levels or at doses below those routinely used in toxicity testing
- **Key conclusions**
 - Sufficient evidence for low dose reproductive and developmental effects
 - Some estrogens exhibit NMDRCs
 - Implications for toxicity testing and risk assessment not resolved

Addressing this Issue: Background (Cont'd)

- **2009 Proposed Endocrine Disruption Prevention Act**
and Congressional inquiry
- **2011 EPA Low Dose Workshop**
 - EPA scientists from Programs (OCSP, ORD (ACE, CSS, HHRA, SHC, SSWR), OW) evaluate the state-of-the-science and implications for dose setting
- **2012 *Endocrine Reviews* article (Vandenberg et al.)**
 - Review of NMDRCs for EDCs
 - Endocrine Society Recommendations
- **2012 International Meetings**
 - Heightened international attention and emerging collaborations (PPTOX III, May 2012, Paris; Low Dose Effects and NMDR, September 2012, Berlin)

Overarching Science Question

Are modifications to standard test guidelines for toxicity testing used in risk assessment needed

- to detect and characterize non-monotonic adverse effects for chemicals?
- particularly those that are mediated by effects on the endocrine system?



Rapid Coordinated Cross Program & Office Response to a Science Issue

- Established cross Office and Program Steering Team
 - Mid-April 2012
- Developed Work Plan
 - Completed Early May 2012
- Establish Cross Office/Program Work Group late July 2012
- Work with cross-agency partners as the product is developed
 - FDA, NTP/NIEHS

EDC NMDRC ANALYSIS

Defined Key Scientific Questions:

- (1) Do non-monotonic dose response curves (NMDRC) exist for chemicals and if so under what conditions do they occur?
- (2) Do NMDRCs result in *adverse effects* that are not captured using our current chemical testing strategies?
- (3) Do NMDRCs provide key information that would alter EPA's current weight of evidence conclusions and risk assessment determinations, either qualitatively or quantitatively?

EDC NMDRC ANALYSIS

- Established key objectives
- Tasks to complete in order to fulfill objectives
 - Actions needed to complete tasks
- Timeline – 6 months from establishment of workgroup

Objectives:

- EPA State of the Science and Position Paper that addresses the 3 questions for external peer review
- Review articles – submit and publish subsequent to the peer review
- Communication – EPA risk managers, external stakeholder outreach

Technical Support for EPA Needs:

As a cross-Agency concern, OCSPP has identified this as a high priority issue and requested that ORD lead the development of the agency position based on the current state of the science

Cross-ORD Program Coordination and Flexibility:

Ability to rapidly address high priority issues. ORD, with its partners, will make a concerted and intensive effort over a short timeframe to ensure that EPA policy decisions are based the best science

Effective Communication:

Internal and external (EPA risk managers and senior leaders, other federal agencies, industry, and the general scientific community)