ORD Science Integration:

EPA's Nonmonotonic Dose Response Curve (NMDRC) Workplan

NMDRC Science Policy Issue: There are divergent positions in the scientific and regulatory communities regarding whether modifications to EPA's standard guidelines for reproductive and developmental toxicity testing and risk assessment are needed in order to detect and characterize low-dose adverse effects of endocrine disrupting chemicals (EDCs). EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) asked for ORD's assistance to resolve this issue.

Highlight of the NMDRC Integration: Use of technical support (i.e., work outside of the existing ORD research portfolios) from multiple ORD Research Programs to rapidly respond to partner needs.

ORD Response: To resolve this controversial issue, ORD appointed a Workplan Steering Committee in April 2012. The accomplishments to date have been:

- Steering Committee appointed by ORD's Deputy AA for Science to Develop Workplan for Resolving EDC Low Dose Issue in 30 days
- Steering Committee Members from Partner Programs (e.g., OCSPP) and ORD Research Programs including CSS, SSWR, SHC, and HHRA.
- Steering Committee reframed the EDC low dose issue to the NMDRC issue
- NMDRC Workplan Developed (May 2012)

NMDRC Workplan: The Steering Committee developed 3 key scientific questions to incrementally resolve this issue. The questions are -

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

The Workplan Objectives are -

1) EPA Position Paper to address 3 questions - externally peer reviewed
2) Review articles - submit to a peer-reviewed journal
3) Communication – including plan, stakeholder outreach strategy, and fact sheets.

In consultation with Program Offices, ORD's Chemical Safety for Sustainability (CSS) Program has led the effort to assemble a NMDRC Working Group of experts in developmental and reproductive toxicology, epidemiology, dose-response modeling, and estrogen (E), androgen (A), and thyroid (T) hormonal pathways to implement the NMDRC Workplan. The next steps are for ORD to assemble an NMDRC Working Group of EPA senior scientist experts in ORD and our Program Office partners to implement the Workplan (anticipated in June 2012).

Four ORD Research Programs, SSWR, CSS, HHRA and SHC, along with Program Offices, will be contributing resources to rapidly develop the state of the science position paper. The timeline

for completion of the literature review and the internal draft of the Position Paper is 6 months from the formation of the NMDRC Workgroup.

EPA is also beginning to engage the FDA and the NTP in order to develop a cross-Agency review and position. The long-term objective of the Workplan is to broaden the scope of the NMDRC investigation to other biological systems beyond the endocrine system.

History:
2000 - EPA and NIEHS held an Endocrine Disruptor Low Dose Peer Review Workshop (http://www.epa.gov/endo/pubs/edmvs/lowdosepeerfinalrpt.pdf) to perform an independent scientific peer review of the available data, including a statistical re-analysis of a number of studies that suggest a NMDRC for EDCs. A key conclusion from the workshop was that there is sufficient evidence for low dose (defined as biological changes, *not limited to adverse effects,* which occur either at human exposure levels or at doses below those routinely used in EPA's toxicity testing) reproductive and developmental effects after exposure to estradiol and a number of environmental estrogens and, further, that some of these estrogens exhibit NMDRCs. However, the implications of the workshop findings for toxicity testing and risk assessment methodologies were not resolved. Since 2000, EPA has been conducting both intramural and extramural research on the topic through ORD labs and centers and the STAR grant program.

2009 – Introduction of the Endocrine Disruption Prevention Act along with Congressional and public inquiry.

2011 – Low Dose EDC Workshop was held with scientist participation from different program offices (i.e., OCSPP, OW) and ORD to review the state-of-the-science and discuss potential implications. The workshop participants emphasized the need for a comprehensive review because the field has been advancing rapidly.

2012 – Publication of review article (Vandenberg et al., 2012) and significant renewed international interest.

Challenges to Integration:

- Scientific controversy that stems from differences in study findings, data gaps and uncertainties.
- Redirection of scientists who had been committed to ORD Program's planned research activities.
- Redirection of resources

Strengths: This example highlights cross-ORD Program coordination and flexibility to enable resolution of a high priority and controversial environmental health issue that is important to our Program Partners and the scientific community. Structuring the activity around a set of manageable, answerable questions is expected to increase the ability to progress incrementally on the issue. As EDC low dose and NMDRC work continues to rapidly develop (i.e., new publications), ORD, with its partners, is making a concerted and intensive effort over a short (6 month) timeframe to ensure that EPA policy decisions are based on current, up-to-date science.

Added Value of Integration:

- ***Serving our Program Partner Needs:*** *Technical Support (outside of the planned research) allows for flexibility to respond to partner needs.*

- ***Cross-ORD Program Coordination and Flexibility:*** *Enables acceleration of high priority environmental health issues.*

- ***Effective Communication*** *(e.g., fact sheets): Enables understanding of the basis for decisions both internally and externally.*

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