Endocrine researchers explore dimensions of dose response

By Eddy Ball

The Duke University Integrated Toxicology and Environmental Health Program held its annual fall symposium Oct. 24 in the Searle Center Lecture Hall.

Speakers at the symposium shared their latest findings involving a new paradigm of nonmonotonic dose response (NMDR) involved in low-dose exposures to hormones and endocrine-disrupting chemicals. The paradigm, which remains controversial, is counterintuitive for classical toxicologists, who point to the contention by Paracelsus, "The dose makes the poison," as a guiding principle.

Supporters of the nonmonotonic paradigm argue that exposure to endocrine-disrupting chemicals at low doses can have significant effects that are not seen at higher dose levels. Advocates point to mechanisms unique to the endocrine system, such as receptor saturation and feedback inhibition, that blunt the effects of higher doses.

"Interpretation of these new [low-dose] results is challenging, particularly within regulatory landscapes and risk assessment frameworks that operate under the assumption of a linear relationship between exposure dose and adverse effect," said symposium chair Heather Stapleton, Ph.D., of Duke University, as she opened the meeting.

Stapleton introduced a program of researchers supported by NIEHS and the U.S. Environmental Protection Agency (EPA), who discussed their findings against a backdrop of two important documents — a draft state-of-the-science paper *(http://epa.gov/ncct/download_files/edr/NMDR.pdf)* written by EPA in June 2013 and the external peer review *(http://www.nap.edu/catalog.php?record_id=18608)* of that paper published by the National Research Council (NRC) earlier this year.

NMDR — looking at dose response through the endocrine lens

"The question is no longer whether nonmonotonic dose responses are 'real' and occur frequently enough to be a concern — clearly these are common phenomena with well-understood mechanisms," Birnbaum wrote in her frequently cited editorial. "Instead, the question is which dose–response shapes should be expected for specific environmental chemicals and under what specific circumstances."

Chemical-specific dose response — an idea whose time has come

Although NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., was unable to attend the symposium, several of the speakers, including NIEHS Chief of Staff Mark Miller, Ph.D., referred to Birnbaum's March 2012 editorial *(http://ehp.niehs.nih.gov/1205179/)* in Environmental Health Perspectives. After a brief review of recent findings on NMDR, her conclusions sounded a note that has resonated throughout the environmental health community (see sidebar).

The first speaker in the program was the acting director of the EPA Office of National Center for Computational Toxicology, David Dix, Ph.D., who presented an "Overview of the U.S. EPA Endocrine Disrupter Screening Program." Dix traced the development of the screening program for hormone receptors over the past two decades and the program's relevance for automated high-speed assays for prioritization of chemicals for toxicology testing.

"We're very happy with the performance of the assays," Dix said. He emphasized that the EPA paper was a draft that will be revised with NRC recommendations in mind, especially the need to integrate human and animal data.

One of the authors of that paper was Miller, who came to NIEHS from EPA in 2013. Miller's presentation, "State of the Science for Non-monotonicity: Asking Better Questions," discussed the framework for the questions posed in the EPA draft review and highlighted the strengths and weaknesses of the report, as identified by the NRC review. He also posed several future questions that should guide upcoming research on NMDR and the EPA's revision of their document, including the perplexing issue of mixtures.

"I want to give credit to the EPA for taking this [NMDR] on in a meaningful way, and committing to appropriately revise this report based on the best available science," he said.

Qualified consensus

With their keynote talks, Dix and Miller established many of the themes that would emerge in the presentations that followed

(see text box). Although this was the kind of scientific meeting in which strong opinions could clash, there was a surprising level of agreement about NMDR and the importance of determining compound-, mixture-, and even tissue-specific dose responses.

However, another of the authors on the EPA paper, Earl Gray, Ph.D., showed more skepticism about the concept in his review of the *in vivo* literature, as suggested by the title he submitted for the agenda, "Non-monotonic Dose Response: Fact or Falderal." Gray pointed to reproducibility and contamination issues, as well as the practice of exhaustively examining just one animal per litter.

"I think we can improve the testing and protocols," Gray argued. He concluded that the studies he reviewed did not indicate that robust, reproducible NMDR curves were common events at low levels.

Also on the program

Four other speakers at the symposium also addressed the central thesis of NMDR — that low doses of numerous stressors cause adaptive and maladaptive responses that can profoundly affect health and treatment outcome.

- NIEHS grantee Laura Vandenberg, Ph.D., *(https://www.umass.edu/sphhs/person/faculty/laura-n-vandenberg)* of the University of Massachusetts, Amherst — "Non-monotonic Dose Response: Under Which Circumstances?"
- NIEHS grantee Edward Calabrese, Ph.D., *(https://www.umass.edu/sphhs/person/faculty/edward-j-calabrese)* of the University of Massachusetts, Amherst — "Biphasic Dose Responses in Biology, Toxicology, and Medicine."
- EPA and National Science Foundation grantee Gerald LeBlanc, Ph.D., *(http://tox.sciences.ncsu.edu/people/gerald-a-leblanc/)* North Carolina State University — "Low Dose Effects and Non-monotonic Dose Responses: Secrets Invertebrates Hold."
- Former NIEHS scientist Robert Chapin, Ph.D., *(http://www.researchgate.net/profile/Robert_Chapin)* now of Pfizer, Inc. — "NMDRs: One View From Industry."

1/6

Stapleton, whose own research interests include endocrine disruption through exposure to fire-retardant chemicals, introduced each of the speakers and organized the panel discussion that concluded the program. (Photo courtesy of Steve McCaw)

2/6

As Dix described the EPA Endocrine Disruption Screening Program, he made the connection between computational toxicology and the ambitious Tox21 predictive toxicology initiative that includes EPA, NIEHS, National Center for Advancing Translational Sciences, and the U.S. Food and Drug Administration as partners. (Photo courtesy of Steve McCaw)

3/6

Miller, right, sat with NIEHS grantee Heather Patisaul, Ph.D., left, and NIEHS grant administrator Jerrold Heindel, Ph.D. Responding to Heindel's question later about why the EPA report team rushed publication of its draft, he said, "If you don't get a draft out, you'll never get a final version out." (Photo courtesy of Steve McCaw)

4/6

Vandenberg, left, and Patisaul listened as Dix described EPA Toxcast prioritization assays. Seated behind them are NTP Tox21 lead Raymond Tice, Ph.D., and senior scientist Richard Paules, Ph.D. (Photo courtesy of Steve McCaw)

- 

5/6

Gray's review pointed to questions about dose response that need to be addressed in future studies. Confounding factors abound, he argued. "It's doubtful you'll ever find a rack in an animal room without phthalates [a group of endocrine-disrupting chemicals]," he said. (Photo courtesy of Steve McCaw)

- 

6/6

Afternoon speakers LeBlanc, center, and Calabrese, right, took advantage of the break to talk with the many students who attended the symposium. (Photo courtesy of Steve McCaw)
