

Birnbaum presents plenary at meeting of Canadian toxicology group

By Eddy Ball

NIEHS and NTP Director Linda Birnbaum, Ph.D., added an interesting twist on the famous quote from Paracelsus during her plenary talk Dec. 4 in Ottawa, "Does dose make the poison? A current assessment of nonmonotonicity."

Addressing the [Society of Toxicology of Canada \(STC\)](http://www.stcweb.ca/en/index.shtml)

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45th Annual Symposium on "Mechanistic Paradigms for Toxicological Regulation," Birnbaum, who was joined by an NTP toxicologist and two NIEHS grantees at the meeting, discussed an emerging paradigm of dose response.

The quote from Paracelsus (1493-1541), who is acknowledged as the father of toxicology, points to the traditional notion of dose response - that increasing dose increases toxicity in a monotonic pattern. "All things are poison," Paracelsus is quoted as saying, "and nothing is without poison; only the dose permits something not to be poisonous."

Increasingly, toxicologists in the field of environmental health science, such as Birnbaum, are recognizing that for some compounds, especially hormones and hormone-like chemicals, the reverse may hold true. In these cases, a much smaller dose may have a disproportionate impact on toxicity, while greater doses may actually blunt effects through several antagonistic mechanisms, including the saturation of receptors.

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

Does dose make the poison?

Birnbaum built the case for her central premise, with examples of essential nutrients, which exercise their beneficial effects at low doses, and hormones, specifically prolactin, which exerts both stimulatory and inhibitory effects upon testicular steroidogenesis. She also outlined eleven mechanisms for nonmonotonic dose response, including tissue-specific shut-off response, biochemical modification of receptors, and endocrine feedback loops.

This complicated and somewhat counter-intuitive concept, Birnbaum noted, has gained increasing acceptance among scientists and regulators. She pointed to a growing body of literature and statements in 2012 and 2013 by The Endocrine Society, U.S. Environmental Protection Agency (EPA), and European Commission Office of the Chief Scientific Advisor. She also referred to an NTP review in 2001 of literature on endocrine disrupting compounds (EDCs).

A central issue in environmental health science, Birnbaum continued, is the low-dose effect of exposure to endocrine disruptors, which the World Health Organization defined in 2002 as exogenous, or external, substances or mixtures that alter the function of the endocrine system. Disruptors include the obvious players - natural and synthetic hormones - but also plasticizing compounds, fire-retardant chemicals, and some pesticides.

A new conversation about endocrine disruption

EDCs can have immediate effects, but their most harmful impacts are often masked or delayed - with exposures during sensitive developmental windows triggering alterations that cause disease in later life, especially in vulnerable individuals and sensitive subpopulations. "Low-dose exposures that seem insignificant may have biological meaning if persistent, bioaccumulative, and/or if exposure is continuous or repetitive," Birnbaum said in her conclusion. "It is not only the dose that makes the poison, but also the timing [of the exposure]."

Referring again to the EPA statement on nonmonotonic dose response earlier this year, Birnbaum reinforced her call for action. "It is time to start the conversation between environmental health scientists, toxicologists, and risk assessors," she said, "to determine how our understanding of low-dose effects and nonmonotonic dose responses influence the way risk assessments are performed for chemicals with endocrine-disrupting activities."



Birnbaum, right, enjoyed an opportunity to talk with STC President Louise Winn, Ph.D., (http://meds.queensu.ca/faculty/louise_winn) of Queen's University, about environmental health concerns common to people in the U.S. and Canada. Birnbaum's elegant argument for expanding perspective on dose response set the stage for the first session of the meeting, which examined future directions in the areas of carcinogenesis and toxicity. (Photo courtesy of David Josephy)

During the question-and-answer portion of her presentation, Birnbaum fielded a range of questions about high-throughput screening of potentially bad actors; replacement chemicals, such as bisphenol S; and applications, as well as implications, of the precautionary principle.



Symposium program chair *Jayadev Raju, Ph.D.*, (<http://www.scirp.org/journal/DetailedInforOfEditorialBoard.aspx?personID=7186>) left, of Health Canada, and Jones shared ideas just before the proceedings commenced. (Photo courtesy of David Josephy)



Auerbach is a molecular toxicologist in the NTP Biomolecular Screening Branch. His primary role is the analysis and interpretation of multivariate data sets. (Photo courtesy of David Josephy)



Josephy described the question-and-answer session following Birnbaum's talk as lively and stimulating. "We need to consider risk-benefit issues," Birnbaum said, in response to one question. "Do we really need particular compounds [that may pose a risk to health] for particular purposes?" (Photo courtesy of University of Guelph)



Gasiewicz discussed a transcription factor that has a critical role in the body's response to toxic exposures. (Photo courtesy of David Josephy)

Supporting the goals of our colleagues to the north

Joining Birnbaum at the meeting were NTP toxicologist [Scott Auerbach, Ph.D.](#), and NIEHS grantees [Dean Jones, Ph.D.](#), (<http://www.systemsbiology.emory.edu/people/investigators/jones-dean.html>)

of Emory University, and [Tom Gasiewicz, Ph.D.](#), (<http://www.urmc.rochester.edu/people/20020354-thomas-a-gasiewicz>)

of the University of Rochester, who is also a member of the [National Advisory Environmental Health Sciences Council](#).

Their talks were prominent, among the 11 presentations during the symposium's three themed sessions:

- Auerbach explored "Characterization and application of toxicogenomic perturbation space," and Jones argued for new directions in toxicology with his talk, "Sequencing the human exposome: a call to action." Their talks were part of session two, "Genome, Epigenome, and Exposome: Future Roles in Carcinogenesis and Toxicity."

- Gasiewicz discussed "The Ah receptor in hematopoietic stem cells (HSCs): regulation of signaling pathways associated with HSC function," as part of session three, "Molecular Toxicology: Mapping the Pathways."

One member of the STC board of directors, incoming president [David Josephy, Ph.D.](#)

(http://www.uoguelph.ca/mcb/people/faculty/faculty_josephy.shtml)

had a special reason to appreciate the contributions of NIEHS scientists and grantees at the symposium. An award-winning molecular toxicologist at the University of Guelph since 1983, Josephy completed a postdoctoral fellowship at NIEHS in 1982.

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