The Low Dose Hypothesis and Non-monotonic Dose Response

What is the Low-Dose Hypothesis?

When evaluating toxicity of chemicals, scientists test a wide range of doses from low microgram levels to thousands of times higher (in the milligrams per day range). In doing so, they seek to identify a threshold at which biological responses are observed, but below which are not concluded harmful. "Low-dose effects" refer to responses that may occur at doses well below those levels previously tested and determined to be safe. The idea that some chemicals can cause a biological response at these low dose levels is called the "low dose hypothesis."

For centuries the basic tenet of toxicology is that the dose makes the poison -- meaning, the larger the dose of a chemical substance, the greater the response in the human body. Moving away from this principle, some researchers have published studies that indicate in certain circumstances different non-linear dose versus response interaction, such as non-monotonicity can possibly occur. These researchers have speculated that a more significant reaction could occur at a low dose as compared to those observed at higher doses. If this hypothesis is scientifically verified, this could impact current regulatory approaches for evaluating toxicity and assessing potential risks.

In 2002, NIEHS/NTP, with expert scientists, conducted a thorough review of the scientific literature of the low dose hypothesis and developed a comprehensive report. Following that review, EPA concluded:

"Until there is an improved scientific understanding of the low-dose hypothesis, EPA believes that it would be premature to require routine testing of substances for low-dose effects in the Endocrine Disruptor Screening Program. EPA recognizes that in the future relevant information may become available on specific chemicals. Such information may support testing for low-dose effects on a case-by-case basis." http://www.epa.gov/endo/pubs/edmvs/lowdosepolicy.pdf

In the 10 years since, considerable research has been conducted, including investigations by EPA and FDA researchers in their own laboratories. To date, this research has not confirmed such postulated "low dose" non-monotonic effects.

Scientific Shortcomings of the Low-Dose Hypothesis

The low-dose hypothesis suffers from numerous scientific shortcomings:

1. There is no broad consensus on the definition of "low dose." It has been used in many ways; a low dose could refer to a level of exposure below what humans are ordinarily exposed to, or a level that is below what regulatory agencies have established for safety testing, or an exposure below a "safe" health guidance value established by an authoritative body. Without a clear definition structured in a manner that is scientifically testable, the low-dose hypothesis cannot be validated.

2. Some scientists claiming to have found evidence in support of the low-dose hypothesis have declined requests to make their underlying data available for independent, scientific verification in a public forum. Data from more than half of the published studies (6 of 11 investigations) were not disclosed by one group of investigators alleging low dose / non- monotonic effects. , Thus, independent scientists were not able to fully examine and independently verify their conclusions. http://ntp.niehs.nih.gov/ntp/htdocs/liason/LowDosePeerFinalRpt.pdf Page A-3

3. Independent and scientifically peer reviewed research conducted by EPA's leading endocrine research laboratory in the Office of Research and Development, published in 2010, was unable to reproduce purported low dose non-monotonic effects.
http://toxsci.oxfordjournals.org/content/114/1/133.full

4. A comprehensive review by an independent panel of experts in 2008 concluded, "There are several large, robust, well designed studies with multiple dose groups using several strains of rats and mice and none of these detected any adverse reproductive effects at low to moderate dosage levels of BPA administered via the relevant route of human exposures."
http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20147/pdf

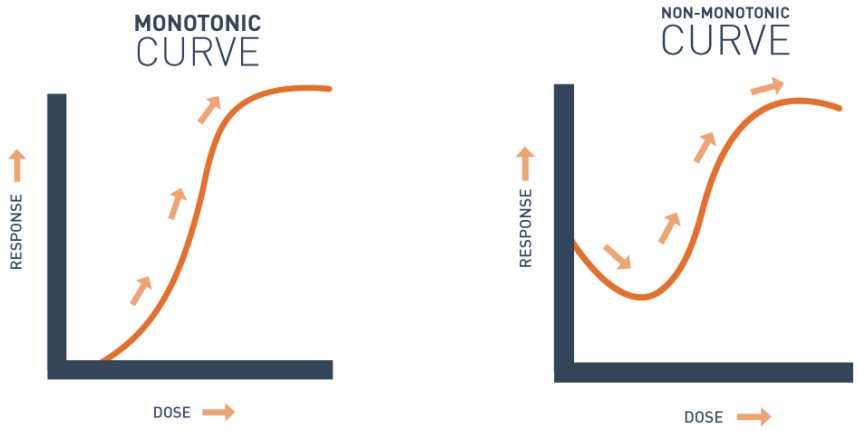
5. An advisory committee of the German Society of Toxicology, evaluating claims of low dose non-monotonic effects and their reproducibility, concluded that "positive results from some explorative studies have not been confirmed in subsequent studies with higher numbers of animals or a priori defined hypotheses"
http://informahealthcare.com/doi/pdf/10.3109/10408444.2011.558487

6. Both US Food and Drug Administration (FDA) and the European Food Safety Agency (EFSA) have concluded that even in cases where biological responses are detected, not all observations at low doses are necessarily adverse or precursors to adverse effects in living organisms.
http://www.efsa.europa.eu/en/faqs/faqlowdoseeffects.htm#4
http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_fda%20bpa%20draft%20assessment.pdf

7. A peer reviewed commentary analyzing the recent paper from proponents of the low dose hypothesis concluded that the authors had clearly overstated the scientific evidence. http://www.sciencedirect.com/science/article/pii/S0273230012001262 The scientific weaknesses included:
    - Inappropriate, selective citation of studies "without examining whether their putative examples are consistent and coherent with other relevant information;"
    - Assuming that "any statistically significant association indicates causation of an adverse effect;"

- Failure to evaluate all studies equally and the lack of uniformity in the evaluation of specific studies (i.e., studies with positive results are evaluated differently than those with null results).
- Lack of documentation as to whether "exposures in studies are truly ''low-dose'' and relevant to humans."
- A large number of examples presented "would be – and indeed have been – questioned by many scientists."

Monotonic vs. Non-Monotonic Dose Response Curves



The principle that the dose makes the poison means that the higher the dose, the greater the effect. The relationship can be linear or non-linear, but in each case, a response curve moves along an upward diagonal, from left to right. This is described as a monotonic response.

For non-monotonic responses, the dose-response curve changes direction somewhere within the range of the doses examined. An 'inverted-U' is a non-monotonic curve, as is a 'U' shaped curve.

Although non-monotonic dose responses are theoretically possible, most observations come from studies in test tubes outside a living organism. Yet some responses have also been reported in intact organisms. Given all of the shortcomings, many scientists continue to question under what conditions they occur and their relevance to hazard and risk assessment for exposures to trace levels of chemicals in our environment.

Implications for Chemical Safety Testing and Risk Assessment

All scientists – those from government, industry and non-government organizations– should agree that decisions about the safety of chemicals in commerce must be based firmly on reproducible scientific studies and the weight of scientific evidence. Currently, the overall weight of the scientific evidence for the low dose hypothesis does not support making radical changes to chemical safety testing or risk assessment methods. At the same time, it is important to investigate new scientific theories such as

non-monotonicity and utilize all scientifically valid, reproducible and relevant evidence to ensure regulatory decisions are based on the best available science.

EPA's Forthcoming Evaluation of Non-Monotonic Dose Responses For Endocrine Active Compounds

EPA is in the process of conducting an up to date review to address the following questions:

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

ACC has requested that the Agency:

- Base it's analysis on up-to-date scientific knowledge.
- Use consistent and scientifically objective data evaluation protocols to evaluate studies (irrespective of who conducted the study, where it was conducted, or who funded it).
- Employ a clear and consistent weight of evidence framework that takes into account, and integrates, all relevant data and information and gives the greatest weight to information from the most relevant and highest quality studies.
- Release the draft report for public review and comment and then subject the report to independent peer review in accordance with acceptable scientific approaches.