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ENVIRONMENTAL EXPOSURES, ENDOCRINE DISRUPTING CHEMICALS, AND NEW APPROACHES TO THE SCIENCE OF RISK ASSESSMENT

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Abstract
Formal risk assessments are largely designed to evaluate individual chemical substance exposures at mostly high doses, and adverse effects in adult animals. Increasingly, toxicologists are recognizing that for some compounds, especially hormones and hormone-like chemicals, a much smaller dose may have a disproportionate impact on toxicity, while greater doses may actually blunt effects through several antagonistic mechanisms. This talk will focus on cutting edge concepts in toxicology as they relate to environmental exposures.

Introduction/Discussion
Formal risk assessment for environmental contaminants, including those for persistent organic pollutants, has traditionally relied on hazard data generated by conventional, laboratory-based toxicity tests[1]. In these toxicity tests animals exposed to toxicants are used to evaluate chemicals (e.g., medicines, food additives, and industrial, consumer, and agricultural products) for their potential to cause adverse health effects. Information from toxicity testing serves as an important part of the basis for public health and regulatory decisions concerning toxic chemicals and human exposures.

Current test methods have been developed incrementally over the past 50 to 60 years and are usually conducted using laboratory animals, such as rats and mice[2]. But we know that chemical effects, particularly endocrine disrupting chemicals (EDCs), are difficult to assess because complex causation may hide the effects of single factors; humans and wildlife are rarely exposed to only one agent; non-specific effects are easily confounded; the level of effect may depend on the exact time of exposure; the totality of the effect may become apparent only years or decades later; and the end result may be affected by compensatory mechanisms.

Methods for systemic review have increased the scientific community's ability to address complex environmental health questions[3]. The goal of systematic review is to objectively and transparently collect and synthesize scientific information to inform decisions, reach conclusions, or identify research needs regarding a specific scientific question[4]. Within the context of environmental health, this requires the integration and evaluation of a broad range of relevant data, including not only traditional laboratory based toxicology studies but also mechanistic data from *in vitro* studies, modeling data from *in silico* studies, and human data from clinical studies, accidental or occupational exposures, and observational epidemiologic studies. By integrating multiple evidence streams in a clearly articulated and consistent manner, scientists can assess a chemical's potential to cause adverse human health effects with greater confidence.

Systematic review allows for increased transparency and the recognition of potential bias but it does not replace the need for scientific judgment. Studies are evaluated and weighted in a systematic review based on their reporting quality, risk of bias, and directness/applicability. Using the results of animal tests to predict human

health effects involves a number of assumptions and extrapolations that remain controversial. For example, test animals are often exposed to higher administered doses than would be expected for typical human exposures, requiring assumptions about effects at lower doses or exposures.

Current assumptions about EDCs and how they affect our bodies are being challenged within the scientific community[5]. Advances in molecular biology, biotechnology, epigenetics, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. Increasingly, toxicologists are recognizing that for some compounds, especially hormones and hormone-like chemicals, a much smaller dose may reveal subtle effects that become masked by the overt toxicity observed at higher doses[6].

Whereas the traditional view is that higher doses are bad and lower does are not as bad, we now know that low-dose effects from some chemicals can have a substantial impact on our health. While there are still many places around the world where the most important problems are excessive exposures to highly toxic heavy metals, pesticides, or other substances, new understanding of how low level, common exposures contribute to the development of common disorders like diabetes, developmental delays, and other modern epidemics, is changing the traditional paradigm of toxicology. It is no longer as simple as "dose makes the poison".

Nonmonotonic dose responses are measured biologic effects with dose response curves that contain a point of inflection where the slope of the curve changes sign at one or more points within the tested range. An increasing number of studies with endocrine endpoints are finding NMDRs[7]. These are of specific concern in the context of chemical testing and risk assessment because they do not follow expected dose response curves, wherein increasing dose is associated with increasing frequency or severity of effect. This is problematic because traditional regulatory toxicology relies on the assumption of monotonicity of biological response in setting reference concentrations or "safe" exposure levels.

We now know that exposure to endocrine disrupting chemicals (EDC) may have activational and/or organizational impacts[8]. By "activational" we mean that an EDC may have direct effects cause by the perturbation of normal endocrine function. These effects are typically transitory and can occur at any point during an individual's lifetime. Organizational impacts can occur when exposure to a small quantity of an EDC, during a specific period of development, or window of susceptibility, can permanently modify the organization of the reproductive, immune, and nervous systems. Typically these effects stem from exposures during the pre- or peri-natal period but may not be observed until puberty and throughout adulthood.

Organizational modifications provide a route through which early life exposure to EDCs may lead to disease states throughout life and adulthood. This concept is referred to as Developmental origins of Health and Disease (DOHaD)[9]. Specific windows of susceptibility provide unique opportunities that may affect physical development, epigenetic gene regulation and/or hormone signaling. Adverse modifications to epigenetic regulatory processes are unique because this non-coding regulation may cross multiple generations from a single parental, grand-parental, or great-grand-parental exposure. Disorders with developmental origins include cardiovascular disease, obesity, type 2 diabetes and metabolic disturbances, osteoporosis, chronic obstructive lung disease, some forms of cancer, and some mental illnesses.

Conclusion

Currently, greater than 85% of non-communicable disease has environmental causes or contributions[10]. The protection of human health and wellness requires strong scientifically-based risk assessments to form the basis for international regulatory decision making. As debate continues in the scientific community regarding how to apply novel concepts related to endocrine disrupting chemicals[11,12], it is evident that an objective and transparent systematic approach that incorporates a broad range of data types and sources is required. The integration of human, animal, and *in vitro* study data, including data with nonmonotonic dose responses, within the "low-dose" range and at the most sensitive time periods, will provide the strongest assessments. Unlike genetic factors, environmental exposure can be modified to support health and wellness. By better understanding the nature of

disease and the factors influencing its incidence and severity, modern science can better empower individuals to make healthy choices.

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