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THOUGHT LEADERSHIP

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Evidence Integration for Health Protection in the 21st Century

Arsenic as a data-rich example

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Rapid growth in life sciences research has fueled efforts to analyze multiple streams of data from studies in humans, animals, and cells or molecules to address complex health issues. These analyses are transforming regulatory assessments of chemicals and pharmaceuticals to better support evidence-based health-protective criteria and approvals for exposures to human populations, including susceptible individuals or subgroups.

Arsenic is an environmental chemical with a wealth of scientific data from epidemiology and experimental toxicology studies—thereby allowing complex evidence integration to assess its health risks in food, water, and soil. For such data-rich substances, two major approaches have emerged for advancing the scientific rigor of and confidence in these more sophisticated regulatory risk assessments: complementary data assessments and systematic literature reviews.

Complementary Data Assessments

First, rather than focusing on identifying the single best human or animal study to estimate a sufficiently low dose without adverse health effects, complementary data streams from various types of studies are used to assess how substances can cause specific human diseases, such as cancer, depending on dose, duration, route of exposure, and other factors. This approach seeks to understand biochemical and molecular mechanisms or modes of action of substances in the body that can lead to health effects, using toxicity tests in cells and genes, in combination with testing in animals and observational data from humans, as envisioned by the National Research Council. Effects such as age, nutrition, variation in chemical metabolism, and other factors are also considered in these analyses to ensure the protectiveness of the findings for sensitive individuals.

A 2019 study demonstrating such a risk assessment for arsenic was sponsored by the Texas Commission on Environmental Quality. In this study, Exponent toxicologists, epidemiologists, and data scientists collaborated with other leading scientists in toxicology, pathology, and epidemiology to assess cancer risks from exposure to arsenic at low doses of relevance for public health protection. This comprehensive study integrated the experimental evidence on how arsenic causes cancer and other toxic effects in cells and animals, along with findings from observational epidemiological studies of humans with elevated arsenic exposure from drinking water. The combined findings from these studies supported a health-protective threshold dose for arsenic in drinking water that was well above the current arsenic drinking water standard of 10 parts per billion.

Systematic Literature Reviews

The second approach to integrating multiple streams of scientific evidence for regulatory risk assessment involves systematic review procedures to search the available scientific literature and evaluate the quality and reliability of studies for use in evidence-based assessments. This strategy has emerged in response to calls for more reliable, reproducible, and transparent methods for assessing the available scientific data. Such systematic literature review methods are increasingly being applied to regulatory assessments for evidence-based evaluation of environmental chemicals and pharmaceuticals. A key component of any such review is identifying studies with reliable data, based on clear and rigorous selection criteria, including transparency of data sources, inclusion/exclusion criteria, and any limitations.

Exponent toxicologists, epidemiologists, and data

scientists recently followed up the 2019 study with a publication on essential concepts in systematic literature review for interpreting and assessing the reliability of arsenic epidemiological studies. In this article, we particularly highlighted spurious dose-response patterns and challenges in interpretation that can arise from statistical aggregation of epidemiological data when estimating human health risks. We used this insight into statistical biases to evaluate the U.S. Environmental Protection Agency's recent dose-response modeling of arsenic and bladder cancer based on eight studies identified from a 2020 systematic review. For example, our findings illustrated how inclusion of epidemiological data classified as being at high risk of bias can skew pooled results combined across studies. Our new publication thus emphasizes the importance of methodological considerations and the potential impact of statistical modeling assumptions on setting science-based regulations to protect human health.

How Exponent Can Help

Our toxicologists, epidemiologists, and exposure and data scientists work together to assess the dose-response for health risks of substances based on rigorous scientific methods and multiple evidence streams, including analysis of mode of action; evidence from toxicology and epidemiological studies; and pharmacokinetic and statistical modeling. These assessments provide the basis for health-protective limits or approvals for substance exposures based on the full weight of the scientific evidence.

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