The National Academies

Division on Earth and Life Studies

Board on Environmental Studies and Toxicology

Unraveling Low Dose Toxicity: Case Studies of Systematic Review of Evidence

SUMMARY: An ad hoc committee under the auspices of the National Research Council (NRC) will develop a strategy for evaluating whether EPA's current regulatory toxicity-testing practices allow for adequate consideration of evidence of low-dose adverse human effects that act through an endocrine-mediated pathway. The study will include a scientific workshop to support the conduct of systematic reviews of human and animal toxicology data for two or more chemicals that affect the estrogen or androgen system. The workshop will seek to identify examples of relevant chemicals, populations/model systems, and end points of interest for further study using systematic-review methods. Systematic reviews for these chemicals/populations/end points for human and animal data streams will be performed under the direction of the committee. The committee will evaluate the results of the systematic reviews, demonstrate how human and animal data streams can be integrated, determine whether the evidence supports a likely causal association, and evaluate the nature and relevance of the dose-response relationship(s). The committee will consider how to use adverse outcome pathway (AOP) or other mechanistic data, including high-throughput data and pharmacokinetic information, to elucidate under what circumstances human and animal data may be concordant or discordant.

POLICY AND BACKGROUND: In May 2014, the National Research Council released *Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as They Apply to Endocrine Disruptors*. The report found flaws with the approaches the agency used to evaluate the evidence on nonmonotonic dose-response (NMDR) relationships and the potential implications for the agency's toxicity-testing strategies and risk-assessment practices. The committee that wrote the report recognized that the scope of EPA's assessment was probably too ambitious for the resources and time available to do a rigorous assessment, and recommended that one option would be for the agency to consider narrowing the scope of its evaluation.

The agency's efforts were in part stimulated by a paper by Vandenberg et al. (2012), which concluded “that when [NMDR] curves occur, the effects of low doses cannot be predicted by the effects observed at high doses. Thus, fundamental changes in chemical testing and safety determination are needed to protect human health.” The paper argues that epidemiologic studies have demonstrated a myriad of health problems linked to low-dose exposures to endocrine-disrupting chemicals and that these effects are not predicted by animal toxicity studies. EPA has asked the NRC to assist in developing a strategy for determining whether low-dose human health effects are being missed by the agency's reliance on current toxicity-testing methods.

The strategy will be based on an evaluation of at least two chemicals that affect the estrogen or androgen system. As advocated in the NRC 2014 report *Review of EPA's Integrated Risk Information System (IRIS) Process*, systematic reviews will be performed to address questions about the relationship between the selected chemicals, populations, and end points. The reviews will be used to support the integration of evidence from human and animal data streams. The nature and relevance of the dose-response relationships, including evidence of NMDR relationships, will be evaluated.

PLAN OF ACTION: Approximately 8 committee meetings will be held; one of the meetings will be held in conjunction with a workshop. Approximately 14 committee members will first be appointed to the committee to plan a workshop and to begin problem formulation. After the case studies are selected, the membership of the committee will be reassessed to determine whether two or more subject matter experts should be added.

Authoritative guidance on performing systematic reviews come from the Cochrane Collaboration (an independent network of groups around the world) and the Centre for Reviews of Dissemination of the University of York, United Kingdom. A representative from one of these groups to serve on the committee will be valuable.

The performance of systematic reviews requires specialized searching, use of software, protocol development, experience in evaluating study designs, and performing statistical analyses. A consultant will be necessary to assist with performing these activities. The literature searches and systematic reviews will be conducted by NRC staff and the consultant working under the direction of the committee.

A committee report will be peer reviewed in accordance with NRC policies and procedures. A prepublication draft of the report will be released 28 months after project initiation, and a final will be published within 2 months of releasing the prepublication. Briefings will be provided to EPA and interested members of Congress. The report will be made available on the National Academies website; other dissemination activities will be planned in consultation with EPA.

Committee members with relevant knowledge and expertise will be sought from academia, industry, consulting firms, and public interest groups. The committee will be formed in accordance with the National Academies policies concerning conflict of interest and bias to ensure a balanced and objective review.

The primary audience for this study is EPA's Office of Research and Development. The

resulting report will also be relevant to other national and international agencies involved in regulatory toxicity testing.

FEDERAL ADVISORY COMMITTEE ACT (FACA)

The Academy has developed policies and procedures to implement Section l5 of the Federal Advisory Committee Act, 5 U.S.C. App., Section 15. Section l5 includes certain requirements regarding public access and conflicts of interest that are applicable to agreements under which the Academy, using a committee, provides advice or recommendations to a Federal agency. In accordance with its Congressional Charter and the requirements of Section 15, the Academy must provide independent, unbiased advice without actual or perceived interference or management of the outcome (findings and recommendations). Therefore, the Academy requires the right to publish all unclassified materials without any restriction over content and release, including any restriction that may require prior approval from the sponsoring agency.

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PUBLIC INFORMATION ABOUT THE PROJECT: In order to afford the public greater knowledge of Academy activities and an opportunity to provide comments on those activities, the Academy may post on its website (http://nationalacademies.org) the following information as appropriate under its procedures: (1) notices of meetings open to the public; (2) brief descriptions of projects; (3) committee appointments including biographies of committee members; (4) report information; and (5) any other pertinent information.

ESTIMATE OF COSTS: The estimated total costs of the project are $1,435,400 over a 30-month period, as seen in the attached estimate.