Strategy for Evaluating Evidence of Low-Dose Toxicity from Endocrine Active Chemicals

Identifying toxic chemicals is important for safeguarding human health. This report outlines a strategy to improve regulators’ ability to evaluate concerns that certain chemicals might cause hormone-related health effects at low doses. Two evaluation approaches of the strategy—systematic review and evidence integration—are demonstrated with data from animals and humans on two classes of endocrine active chemicals. These examples illustrate cases where the evidence supports low-dose effects in people.

Endocrine active chemicals (EACs), also known as endocrine disruptors, are a class of chemicals capable of interfering with endocrine (or hormone) systems. They are of particular concern because they have the ability to alter normal hormone function, and even small changes in hormone concentrations, particularly during sensitive life stages, can have lasting effects. The U.S. Environmental Protection Agency (EPA) regulates EACs and other toxic chemicals as part of its mission to protect human health and the environment. Traditional toxicity testing relies heavily on animal studies that expose test animals to chemicals at amounts (doses) much higher than typical human exposures (i.e., low doses). Whether current regulatory toxicity-testing practices are adequate for identifying low-dose EAC effects is a question EPA would like to address.

EPA asked the National Academies to convene an expert committee to develop a strategy for evaluating evidence of low-dose effects of EACs. The committee developed an overarching strategy and evaluated two chemical classes as a demonstration of how parts of this strategy could be implemented.

PROPOSED STRATEGY

The committee developed a strategy for evaluating evidence of low-dose effects of EACs that involves three broad phases: surveillance, investigation and analysis, and actions (Figure 1). EPA is already conducting many activities consistent with the proposed strategy, although not necessarily in the context of assessing low-dose exposure to EACs.

Surveillance

The purpose of the surveillance phase is to detect signals that raise questions about the potential low-dose toxicity of a particular EAC or about the ability to detect low-dose toxicity more generally. For example, signals might include an indication that an adverse outcome in a human population could be related to an EAC exposure, or evidence that a particular low-dose effect may not be detectable with traditional animal-based toxicity testing.

The committee recommends that EPA develop an active surveillance program focused specifically on low-dose exposures to EACs. As part of this surveillance effort, the committee recommends that EPA regularly monitor data on specific chemicals, information that could have implications for toxicity-testing methods and best practices for EACs, and information on endocrine-related human diseases. Such information could be obtained by conducting regular surveys of the scientific literature, gathering input from stakeholders, and collecting information about human exposure to EACs.
Once signals are identified, EPA can conduct scoping exercises to prioritize areas for investigation and analysis and then formulate key questions to address.

**Investigation and Analysis**

Once a chemical or topic is prioritized for investigation and analysis, the committee recommends EPA select analytical approaches and tools on a case-by-case basis, guided by the questions under study. Four possible approaches, which may be used alone or in combination, include the following:

- **Targeted Analysis**, a method for analyzing (or reanalyzing) data.
- **Generation of New Data or Models** to fill knowledge gaps by pursuing new studies or creating new computational models for analysis.
- **Systematic Review**, a rigorous assessment method that maximizes transparency and consistency through a careful crafting of the research questions and advance planning of the methods used to screen and analyze the available evidence.
- **Integration of Evidence**, a method for using available evidence to draw conclusions. The method can be used to address chemical-specific questions, such as whether a particular EAC poses a hazard to human health, or broader questions, such as whether a new indicator of toxicity is relevant for determining low-dose effects.

**Actions**

Once the investigation and analysis phase has been completed, the next step is to select the action or actions warranted. Examples of potential actions include updating chemical assessments, continuing to monitor for new data, updating toxicity-testing designs and practices, or requiring new data or models to reduce uncertainties. The type of action that EPA takes could be influenced by existing policies and regulations, the size of the population at risk, the public health significance of the human health effects, the availability of resources, and other factors. Making recommendations about what actions to take was beyond the scope of this committee’s activities.

**EXAMPLE REVIEWS CONDUCTED BY THE COMMITTEE**

Two options in the investigation and analysis step of the strategy are approaches that EPA specifically requested the committee demonstrate—systematic reviews of at least two EACs and integration of evidence from animal and human studies.

The two EACs chosen were phthalates and polybrominated diphenyl ethers (PBDEs). The committee selected these EACs based on stakeholder input, surveying the scientific literature, and collecting information about animal and human exposure to several candidate chemicals. These chemicals are known to interfere with hormone pathways, human exposure to them has been well documented, and they have been well studied in animals and humans. Before undertaking its reviews, the committee developed key questions about the effects of the selected chemicals and then developed systematic review protocols to answer those questions.

In its systematic reviews, the committee categorized the overall level of evidence for a health effect as being inadequate, low, moderate, or high. In its integration of evidence step, the committee used these level-of-evidence ratings, along with information about the study question was drawn.

**What is a systematic review?**

A systematic review is an investigation method designed to answer a specific question through a review and assessment of the scientific literature. A protocol is developed to specify the scientific methods that will be used to identify, select, assess, and summarize the findings of studies. Such methods include documentation of the databases to be searched, the criteria that will be used to select studies, and the statistical approaches that will be used to analyze data. These methods help to ensure that studies are evaluated consistently and to document how the answer to the study question was drawn.
potential biological mechanisms involved, to classify the hazard associated with a given chemical as not classifiable, suspected, presumed, or known (Figure 2).

**Example 1: Phthalates**

The first review focused on phthalates, a class of ubiquitous environmental contaminants. Phthalates are known to affect the androgen hormone system, which plays a critical role in the development of the male reproductive tract. The committee conducted separate systematic reviews of the animal and human evidence on phthalate reproductive effects and then integrated the evidence to draw conclusions about potential hazards, low-dose effects, and the adequacy of toxicity-testing methods for evaluating those hazards.

The committee analyzed the evidence related to multiple phthalates and multiple end points related to male reproductive-tract development. One part of this analysis focused on the effects of in utero exposure to diethylhexyl phthalate (DEHP) on anogenital distance (AGD), an indicator of reduced fetal androgen production. Meta-analyses of the animal and human studies found consistent evidence of reductions in AGD in males after fetal exposure to DEHP. Thus, the systematic reviews and evidence integration supported a conclusion that in utero exposure to DEHP is presumed to be a reproductive hazard to humans. This conclusion was further supported by other studies that suggested a plausible biological mechanism for such effects.

The committee found that current toxicity-testing methods can identify a hazard that is presumed to be of concern to humans, but current methods might not be able to accurately predict exposures at which humans are affected. The finding also provides additional support for EPA’s decision to include AGD measurements in regulatory toxicity testing.

**Example 2: PBDEs**

The second review focused on polybrominated diphenyl ethers (PBDEs), another class of ubiquitous environmental contaminants. For this review, the committee analyzed the evidence related to multiple PBDEs focused on whether developmental exposure to PBDEs affect neurobehavioral function. To assess the evidence from studies in animals, the committee conducted its own systematic review of outcomes related to learning, memory, and attention. To assess the evidence from studies in humans, the committee updated a recent systematic review, shared with the committee in draft form, that evaluates effects on intelligence, attention deficit/hyperactivity disorder, and attention-related behavioral conditions.

One part of the committee’s review focused on the effects of developmental exposure to BDE-47 on learning and intelligence. A meta-analysis of animal studies found consistent evidence of decrements in one measure of learning, and a meta-analysis of human studies found an association between PBDE exposure and a decrease on IQ. The committee concluded that BDE-47 is a presumed hazard to humans with respect to effects on intelligence. As with the
Lessons Learned

Lessons learned from conducting the two example reviews shed light on how available evidence can be used to draw conclusions about low-dose exposure to EACs, point to some important gaps, and offer insights to using the overall strategy to help EPA evaluate its toxicity-testing methodology going forward. For example, the committee demonstrated that meta-analyses of animal data were useful for assessing confidence in the evidence and helped characterize dose-response relationships. The process of conducting the example reviews also underscored the importance of taking a multidisciplinary approach to data analysis, raised the need for more consistent reporting of study methods to facilitate evaluation of the risk of bias, and pointed to the challenges associated with integrating data from human and animal studies.

Question: Is developmental exposure to PBDEs associated with effects on neurobehavioral function?

Example chemical examined: BDE-47

Example end point examined: Learning in animals and intelligence in humans.

Level of evidence conclusions: There is a moderate level of evidence that exposure to BDE-47 is associated with decrements in learning in rodents and decreases in IQ in humans.

Hazard classification conclusion: Overall, the evidence supports a conclusion that BDE-47 is a presumed hazard to humans with respect to effects on intelligence. This conclusion means that there was sufficient animal and human evidence to allow the committee to conclude that BDE-47 is a potential hazard to human health. Identifying the potential of a chemical to cause particular forms of toxicity in humans does not indicate whether the substance poses a risk in specific exposed populations. Such a determination requires the completion of a risk assessment that takes into consideration exposure of a given population; a risk assessment was not performed by the committee.

For More Information . . . This Consensus Study Report Highlights was prepared by the Board on Environmental Studies and Toxicology based on the Consensus Study Report Strategy for Evaluating Evidence of Low-Dose Toxicity from Endocrine Active Chemicals (2017). The study was sponsored by the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project. Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242; http://www.nap.edu or via the Board on Environmental Studies and Toxicology web page at http://www.nationalacademies.org.