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Evaluating low-dose toxicity from endocrine active chemicals

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A new report by the National Academies of Sciences, Engineering, and Medicine proposes a strategy that the U.S. Environmental Protection Agency (EPA) should use to evaluate the evidence of adverse human health effects from low doses of exposure to chemicals that can disrupt the endocrine system.

Endocrine active chemicals (EACs) or endocrine disruptors can cause a variation in normal hormone function. Even small alterations in hormone concentrations, particularly during embryonic development, can have lasting and significant effects. Some EACs have the potential to impact human health at lower doses than those used in traditional toxicity testing by the agency, which means that some effects may be missed.

The report's proposed strategy has three broad steps that can help evaluate evidence of impacts from low-dose chemical exposure:

- Surveillance—Surveillance can detect signals of possible health effects by actively monitoring new data, scientific literature, nontraditional information sources, and stakeholder input to ensure health effects are being identified and analyzed on a regular basis.
- Investigation and Analysis—To further investigate the signals, the agency should analyze existing data, generate new data to fill gaps, conduct a systematic review of evidence, or integrate evidence from human and animal studies. One or more of these options might be needed to answer questions about potential

signals.

- Action—Possible actions the agency could take include updating chemical assessments, regularly monitoring for new data, requiring new data or models to reduce uncertainties, or updating toxicity-testing designs and practices. Additional considerations, such as the public health significance and available resources, would also factor into the decision making.

If the results of an investigation suggest that adverse outcomes in humans are expected or might be occurring at low levels of exposure from EACs, the conclusions of previous toxicity assessments might need to be updated to reflect the new evidence. - Additionally, toxicity-testing practices might need to be updated as new data are generated. While EPA is already conducting many activities consistent with the strategy proposed in this report, its efforts may not be aimed specifically at evaluating low-dose toxicity testing, said the committee that conducted the study and wrote the report.

In addition to developing a strategy, the committee was also charged with conducting systematic reviews of animal and human toxicology data for two or more EACs to demonstrate how the results can be integrated and considered with other relevant data to draw conclusions about causal associations. The committee chose phthalates and polybrominated diphenyl ethers (PBDEs) for the reviews. These reviews follow protocols designed to screen and analyze the scientific literature to answer a specific research question. The committee also illustrated how to integrate human and animal data streams, determine whether the evidence supports a likely causal association, and evaluate the nature and relevance of the relationship between exposure and response.

"The systematic review examples demonstrate how these approaches could be used in a strategy to evaluate low-dose toxicity of EACs and also to identify lessons learned that could help EPA employ these

methods successfully," said David Dorman, professor of toxicology at North Carolina State University and chair of the committee.

Phthalates are ubiquitous environmental contaminants and are found in a wide variety of consumer products, including toys, cosmetics, pharmaceuticals, and building and construction materials. Human exposure to them is well-documented, as noted in a 2008 Academies report that called for a cumulative risk assessment of phthalates. The systematic reviews in this report examined the effects of phthalates on male reproductive-tract development in laboratory animals and humans. The reviews focused how the exposure impacted three areas: anogenital distance (AGD)—distance between anus and genitalia, fetal testosterone levels, and cases of hypospadias—malformation of the penis.

One example from the reviews showed that exposure of the fetus to diethylhexyl phthalate (DEHP)—a type of phthalate used as a plasticizer - is presumed to be a reproductive hazard to humans because it is associated with decreased AGD and testosterone levels in males. The evidence of an association between DEHP and hypospadias was not as strong.

In the second set of reviews, the committee examined the effects of PBDEs—used as flame retardants—on developmental neurotoxicity. Just like phthalates, PBDEs are also commonly found in the environment. The review of human studies evaluated the effects of PBDEs on intelligence and attention deficit hyperactivity disorder (ADHD). For the animal studies, tests of learning or memory were considered to have the closest parallels to intelligence measured in human studies and attention tests for ADHD in humans. The committee concluded that there was sufficient evidence that shows PBDEs are a presumed hazard to humans with respect to effects on intelligence.

Both these cases show that current toxicity tests can identify a hazard

that is presumed to be of concern to humans, but they may not be able to accurately predict the specific level of exposures at which humans are affected. Additional pharmacokinetic information—movement of chemicals within the body—is needed in order to better evaluate an EAC's potential to cause health effects in humans at low doses.

As recommended in the committee's proposed strategy, systematic reviews can be an important component in investigating evidence on low-dose adverse effects, and EPA can build on existing systematic reviews that are published in peer-reviewed literature. The committee also recommended performing meta-analyses of the animal and human evidence when appropriate. This statistical method allows data from several studies to be combined and should be used to evaluate confidence in the body of evidence and to characterize the relationship between exposure and response.

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