Message

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Subject: FW: News Update: EPA Appears To Broaden Scope Of NAS' Low-Dose Tox Testing Committee (Inside EPA

FYI-this is an important read. These are some of the issues that Tom was talking about at the STPC meeting that I listened into recently. They now have some context....such as the issue of threshold.

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Subject: News Update: EPA Appears To Broaden Scope Of NAS' Low-Dose Tox Testing Committee (Inside EPA

DAILY NEWS

EPA Appears To Broaden Scope Of NAS' Low-Dose Tox Testing Committee

Posted: October 15, 2015

EPA Science Advisor Thomas Burke appears to be asking a National Academy of Sciences (NAS) panel charged with studying whether the agency's chemical toxicity testing approach sufficiently addresses potential risk to humans and wildlife from exposures to low doses of endocrine active chemicals to consider issues beyond its original charge.

"I know that much of the thought for this committee and some of the words in the statement of task are really focused toward endocrine-mediated effects. But are the effects that we see in endocrine-mediated effects, are they relevant, are the approaches, is the science relevant to other kinds of endpoints?" Burke said Oct. 13 at the NAS panel's first meeting. "For example, one of our biggest challenges is neurodevelopment and neurological effects."

In addition to asking the committee to think beyond the endocrine effects that are a focus of the committee and its charge questions from the agency, Burke also encouraged the committee members to think beyond the mere data and consider its use in regulatory and public health decisionmaking at EPA.

One committee member, Weishueh Chiu, a toxicology professor at Texas A&M University and a former EPA risk assessor, asked Burke, "It's not the narrow question of 'Is this test adequate?' it's more the larger question . . . also the use of the data?"

"That's the hope," Burke replied.

Burke and EPA colleagues met with the committee EPA is sponsoring to consider whether the agency needs to change its regulatory testing and risk assessment approaches in response to concerns that the status quo misses important health risks that occur from

routine, low exposures that are regularly encountered in the environment. The committee follows an earlier NAS panel that reviewed an EPA white paper on a similar topic, non-monotonic dose-response curves.

The 2014 NAS committee urged EPA to redo its draft paper that found that the agency's current test methods are adequate to account for the unusual non-monotonic dose-responses of some chemicals, finding that EPA's scientific review practices were too shoddy for the agency to be able to justify its conclusions. NAS' critical review was EPA's impetus to create this new committee.

"I realize there's some history before us with the agency and nonmonotonic work and . . . the academy's review of that," Burke said. "Hopefully now we're moving forward and getting a better handle on the science and particularly asking the right questions."

Data Types

Burke and colleagues acknowledged that there can be differing results from different types of data, and that sometimes effects are seen in human epidemiology data that are not seen in animal toxicology data, but the animal data are more often used as the basis for EPA decision-making because it is easier to use in regulatory risk assessment and decision-making. Such circumstances seem to further advance questions about low-dose effects and their adversity.

The Endocrine Society and other critics have charged that toxicology tests upon which EPA and other agencies base their assessments of some chemicals' human health risks could be missing effects that are not occurring at the relatively high doses traditionally used in regulatory toxicology testing. They are increasingly concerned that nonmonotonic chemicals that can disrupt the hormone, or endocrine, system may be less predictable by existing testing methods because their dose-response curves can change direction and may not follow the predictable upward slope seen in many chemicals' dose-response curves.

Current EPA test methods do not account for such outcomes and could incorrectly predict chemicals' risks, they say. Several of the society's members also faulted the agency's draft white paper for misrepresenting key studies the researchers conducted, leading to flawed conclusions in the draft white paper.

Burke challenged the NAS committee, saying that members have "an opportunity to transform the way we think about chemical safety science. It's an enormous opportunity, really, to present the information in a new way."
Burke further broadened his expectations for the committee by raising questions about the traditional design of regulatory risk assessments, and suggesting the committee consider aspects that remain thorny for risk assessors, such as the validity of a safe threshold for evaluating doses, dose levels in regulatory testing, the complexity of cumulative exposures along with the population's makeup.

'Right Endpoints'

"It's been pointed out in much of the literature that maybe we're not looking at the right endpoints. Let's face it, an awful lot of regulatory science has been dominated by a small number of endpoints. Some would say that carcinogenicity really held sway in the regulatory arena for almost three decades . . ." Burke said.

"This also challenges us to look at the study design limitations for evaluating doses that are in the range of human exposure. I think it also challenges us to think about threshold. Are we going to continue to think about the toxicity data from high exposure studies in terms of bench mark dose dose and the assumptions of threshold and how do we factor into that the low dose, multiple exposure issue and population variability and susceptibility," he added.

Burke also encouraged committee members to consider the question of cumulative exposures, saying that he hoped this issue would be on committee members' radar as they select the two chemicals for case studies that will address how best to perform a systematic review of evidence. Systematic review is a method for collecting and evaluating scientific literature, intended to answer specific questions in a transparent and methodical way that has gained traction at EPA and more broadly in the environmental health world in recent years.

The charge asks the committee to perform two such reviews of two chemicals, applying the agency's questions about low dose effects to the data for these example chemicals. The committee is also tasked with conducting a public workshop on relevant topics, expected to take place in 2016

Committee Charge

Committee members peppered Burke and his EPA colleagues David Dix, director of the agency toxics office's policy shop, and Tina Bahadori, director of the research office's chemical safety research program, with questions about the charge.

Ruthann Rudel, director of research at the Silent Spring Institute, pressed them to provide suggestions of chemicals that EPA would like to see the committee to perform the systematic reviews of. Burke indicated that the trio would do so.

Another committee member, Sheela Sathyanarayana, an associate professor of pediatrics at the University of Washington's medical school, questioned the EPA representatives about their definition of adverse effects -- an important issue to the broader debate over endocrine-mediated effects.

Endocrinologists have been reluctant in their definitions of effects to define adversity, arguing that some effects, particularly at early or otherwise susceptible developmental stages, may not show evidence of adversity until later in life. But toxicologists have pushed for specificity in the definition, as these determinations are necessary to toxicology testing practices.

EPA, in its draft white paper, concluded that there is sufficient evidence to acknowledge that nonmonotonic dose responses exist, and effects caused by these chemicals exist, but that does not require altering the existing regulatory toxicity testing regime because many of the resulting effects were adaptive rather than adverse, Bahadori said.

'Adaptive' Effects

Bahadori reminded the committee members of EPA's conclusion in the draft white paper that "very senior toxicologists evaluated this issue . . . and opined that the majority of those effects are not adverse at low dose, they're adaptive," adding that "those are the words that we have to work with."

Chiu, however, noted that this was an issue raised in the NAS review of the white paper, which, he said, indicated that EPA's review left out context. "There are comments about issues with the definition of adverse and lacking context and that effects may not be adverse in one person are in another person, depending on lifestage, susceptibility, etc.," Chiu said. "That was raised in the [NAS] review."

Burke acknowledged that the adverse effect definition remains an issue that the committee will grapple with.

Committee chairman David Dorman, a toxicology professor at North Carolina State University, asked EPA representatives where they see the weaknesses in their current strategies -- places that that the committee could provide assistance with.

Dix replied that while the agency has robust methods for incorporating animal toxicity data into risk assessment, staff are at the early stages with alternative toxicity data and also at the very early stages of incorporating human epidemiology data. -- *Maria Hegstad* (mhegstad@iwpnews.com)

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