Message

From: Sonawane, Bob [Sonawane.Bob@epa.gov]
Sent: 7/12/2015 3:49:20 PM
To: Martyn Smith [martynts@berkeley.edu]
CC: Luoping Zhang [Luoping@berkeley.edu]; Birnbaum, Linda (NIH/NIEHS) [E] [birnbaumls@niehs.nih.gov]; Bussard, David [Bussard.David@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]
Subject: Re: News Update: Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment (InsideEPA)

Dear Martyn,

Thanks for sharing the information, very much appreciated.

Bob

From: Martyn Smith <martynts@berkeley.edu>
Sent: Saturday, July 11, 2015 11:26 PM
To: Sonawane, Bob
Subject: FW: News Update: Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment (InsideEPA)

FYI

From: Martyn Smith <martynts@berkeley.edu>
Date: Wednesday, July 8, 2015 at 5:47 PM
To: "'Birnbaum, Linda (NIH/NIEHS) [E]'" <birnbaumls@niehs.nih.gov>
Cc: Luoping Zhang <luoping@berkeley.edu>
Subject: RE: News Update: Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment (InsideEPA)

Dear Linda

Thanks for sending this on. We are in communication with the reporter for this story. Just so that you know the full story, I outline below our perspective of the issue with appropriate references to our publications and funding.

1) We have always said the findings in Zhang et al. 2010 (PMID 20056626) should be replicated – In the paper itself we said that "*Future studies should aim to replicate these findings and examine additional chromosomes, such as chromosome 5, which is also commonly altered in myeloid leukemias* ……" To be honest, I wish we hadn't used the term replication, as it is not really possible to replicate an observational epidemiology study; one can really only add further to the literature.
2) We did go on, however, to expand the previous study to examine more subjects (n=52) in Lan et al. 2015 (PMID 25391402) and examined all 24 human chromosomes (1-22, XY) in the circulating stem/progenitor cells (a CWAS approach). In the process of the expanded study, we replicated our earlier finding of monosomy 7 in a larger number of subjects and showed structural and numerical aberrations in chromosome 5 were also significantly increased. Aberrations in both chromosomes 5 and 7 are frequently observed in myeloid leukemia, particularly, chemically-related AML. In Lan et al. 2015 we also **effectively countered in the *Discussion* all of the critiques** in Gentry et al. 2013 (PMID 23902349).

3) Please note that the funding sources in both Zhang et al. 2010 and Lan et al. 2015 (Dr. Zhang, the corresponding author) papers are acknowledged as "This study was supported in part by the Intramural Research Program of the NIH (National Cancer Institute) and by the **National Institute of Environmental Health Sciences grants R01ES017452 (L. Zhang) and P42ES004705 (M.T. Smith)**." R01ES017452 was awarded to Dr. Zhang (UC Berkeley) under the 2-year ARRA and was the source of funding to perform the complete chromosome analysis (CWAS) at Berkeley. P42ES004705 paid part of my salary and the effort for my participation in this project.

4) To investigate potential mechanisms of formaldehyde-induced leukemogenesis, Dr. Zhang and her collaborators in China further examined bone marrow toxicity in animal models and reported (Ye et al. 2013, PMID 24136419) that exposure to formaldehyde via *nose-only* inhalation can induce DNA-protein crosslinks (DPC), oxidative stress (ROS, MDA) and GSH depletion in mouse bone marrow and peripheral blood. In a separate study (Zhang Y et al. 2013, PMID 24040369), they also confirmed that bone marrow toxicity and oxidative stress occurred in mice exposed to formaldehyde inhalation. Additionally, Zhang reported formaldehyde-induced hematotoxicity, as decreased blood cell counts, occurred both in mice (Zhang Y et al. 2013) and in exposed workers (Zhang et al. 2010).

5) We have also studied early immune/inflammatory effects of formaldehyde on occupationally exposed workers and found that exposed workers experienced decreased counts of NK cells, regulatory cells, and $CD8^+$ effector memory T cells (Hosgood et al. 2012, PMID 22767408) and found significantly lower circulating levels of two chemokines in a later study (Seow et al. 2015, PMID 25908645). These findings suggest that immunosuppression may be associated with formaldehyde exposure.

All the best and see you next week,

Martyn

From: Birnbaum, Linda (NIH/NIEHS) [E] [mailto:birnbaumls@niehs.nih.gov]
Sent: Tuesday, June 30, 2015 6:43 PM
To: martynts@berkeley.edu
Subject: Fwd: News Update: Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment (InsideEPA)

As promised
Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: birnbaumls@niehs.nih.gov

Begin forwarded message:

From: "Sonawane, Bob" <Sonawane.Bob@epa.gov>
Date: June 30, 2015 at 9:43:44 AM EDT
To: "Birnbaum, Linda (NIH/NIEHS) [E]" <birnbaumls@niehs.nih.gov>
Subject: News Update: Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment (InsideEPA)

RISK POLICY REPORT - 06/30/2015

Appropriators Criticize EPA's Pending Draft Formaldehyde Risk Assessment

Posted: June 29, 2015

House and Senate appropriators are highlighting EPA's pending human health risk assessment of formaldehyde to reiterate long-standing concerns about the agency's Integrated Risk Information System (IRIS), calling in fiscal year 2016 appropriations bill report language for increased scrutiny of a controversial study underpinning the assessment.
In its recent update to its public schedule for its IRIS assessments, EPA indicated that its long-running assessment of formaldehyde is in step 4a, where staff is preparing the draft assessment for public release, peer review and comment. But the schedule did not provide a date for release of this draft -- merely stating that staff is addressing the recommendations in 2011 from the National Academy of Sciences (NAS) regarding EPA's earlier draft of the assessment.

But both House and Senate reports suggest that a public draft may be released next fiscal year, saying, "The [NAS] has acknowledged that reproducibility of research results is fundamental to the scientific process. The Committee understands that EPA is likely to include the findings of the Zhang et al (Cancer Epidemiol Biomarkers Prev; Jan; 19(1):80--88) study for scientifically significant decisions in fiscal year 2016. The study, however, has drawn criticisms about its methods and interpretations." *Relevant documents are available on InsideEPA.com. (Doc. ID: 182250)*
EPA in its last public draft IRIS assessment relied on the Zhang study, so-known because its lead author is University of California Berkeley research professor Luoping Zhang, to decide that formaldehyde was a leukemogen. The study was also among the reasons that members of an International Agency for Research on Cancer (IARC) committee voted in 2009 that there is "sufficient evidence" to find there is a causal association of formaldehyde with leukemia in humans.

The unique study of 25 Chinese industrial workers exposed to formaldehyde on the job, however, has raised concerns from industry groups and others who questioned Zhang's findings. The study found key changes in the blood of some exposed to formaldehyde at work.

Critics argue that the epidemiological case for formaldehyde causing systemic cancers like various types of leukemia is weak. Industry and others generally base this argument on a 2003 study of some 14,000 British industrial workers, which does not show risks for various leukemia types. In addition, they argue, there is no reasonable mechanistic explanation for how formaldehyde could cause such systemic diseases, and they have pointed to publications from the lab of James Swenberg, a research professor at the University of North Carolina Chapel Hill. Swenberg and colleagues have performed a series of studies seeking to determine how formaldehyde could cause leukemia, and his studies suggest there is no known mechanism by which this could occur (*Risk Policy Report*, Aug. 3, 2010).
But the Zhang study was also used in the National Institute of Environmental Health Sciences' monograph on formaldehyde in its 2011 Report on Carcinogens. A separate 2014 NAS report reviewing the formaldehyde monograph found there is "largely consistent and strong" evidence supporting a genotoxic and mutagenic biological mechanism for myeloid leukemia, a conclusion that seemed contradictory to that of the 2011 NAS committee critically reviewing the IRIS assessment. Such an endorsement could support an EPA decision to use a conservative linear cancer modeling approach, which assumes that there is no safe level of exposure to the chemical, and it has spurred further research and analysis from industry-sponsored scientists (*Risk Policy Report*, Aug. 12).
Thus, the House report calls it "crucial" to validate the Zhang study's findings, and the Senate report says it is "important" to do so.

But the House, in an unusual move, calls for further action from EPA on the Zhang study, directing the agency to "develop a peer-reviewed protocol to replicate the scientific findings of this study. Following development of the protocol, the Agency is directed to issue a request for proposals and award a contract to conduct this replication study. Further, EPA is directed to incorporate the results of the replication study into any draft or final scientific assessments prior to making such assessments publicly available."

An EPA spokeswoman did not return a request for comment on the report language by press time.
The request is not the first time that someone has suggested replicating the unique Zhang study. When EPA's IRIS program hosted a workshop last year on formaldehyde, more than one researcher called for an attempt to replicate the Zhang study -- but without directing EPA to do it. Several speakers at the April 2014 meeting described the Zhang study as revolutionary, saying it changed their views on whether formaldehyde causes leukemias or just the rare -- and less risky -- nasal cancers seen in lab animal studies.

"The Zhang study was a game-changer," said Leslie Stayner, an epidemiology professor at the University of Illinois-Chicago. Calling it "such a small, simple study," he said that "it needs to be replicated."
He was joined in that opinion by Bernard Goldstein, a professor emeritus at the University of Pittsburgh, who said before the publication of the Zhang study that he thought the epidemiology studies provided weak evidence of formaldehyde exposure causing leukemia. He said having read the Zhang study, he now believes that formaldehyde is probably a leukemogen.
Jim Collins, an epidemiologist with Dow Chemical Company, called the formaldehyde epidemiology studies "not convincing" that formaldehyde is causing leukemeias. "Why don't you replicate the Zhang study?" he asked rhetorically. "Until we do, we'll keep arguing forever" (*Risk Policy Report*, May 6, 2014).
The Senate report addresses its concerns with a different approach, directing EPA "to ensure that the Science Advisory Board Chemical Assessment Advisory Committee [SAB CAAC] specifically addresses the strengths and limitations of the Zhang et al. study during their peer review and takes this evaluation into account in their review of the total body of evidence for the carcinogenicity of formaldehyde."

EPA in its schedule update indicated that its new SAB CAAC would peer review the draft assessment of formaldehyde. The advisory committee was created after NAS' critical 2011 review of the last draft IRIS assessment of formaldehyde's human health risks. The report included a now-famous extra chapter outlining recommendations intended to improve all IRIS assessments, not just formaldehyde.

The Senate report refers to this set of recommendations, found in Chapter 7 of the 2011 NAS formaldehyde report. "The Committee appreciates the work of the Agency to implement the 2011 [NAS's] Chapter 7 recommendations for the [IRIS], but is concerned that the recommendations have not been fully implemented," the Senate report states. "In an effort to ensure that the IRIS program uses the best available science, the Committee encourages the Agency to implement the Chapter 7 recommendations as soon as possible."
The report provides specific elements of concern, relating to "transparent frameworks for problem formulation; processes for study selection, particularly data quality and relevance; use of a robust weight of the evidence process for applying scientific findings; and, apparent continued reliance on default linear modeling approaches to hazard determinations."

The last is a reference to EPA's default use of conservative linear approaches to model cancer potency, a science policy choice the agency makes in assessments where the chemical at issue has a mutagenic or unknown mode of action, meaning how the chemical causes cancer. -- *Maria Hegstad*