Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 8/27/2015 1:07:11 PM
To: Cogliano, Vincent [cogliano.vincent@epa.gov]; Kurt Straif [StraifK@iarc.fr]
Subject: Re: New way to delay our formaldehyde assessment

Wonderful- and is this yet another unfunded mandate from would-be detractors on the Hill? Nonetheless, it's good press for our friends in Berkeley.
Warm regards,
Kate

From: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Date: Thursday 27 August 2015 14:44
To: Kurt Straif <StraifK@iarc.fr>, Kate Guyton <guytonk@iarc.fr>
Subject: New way to delay our formaldehyde assessment

Begin forwarded message:

From: "Bland, Naseera" <Bland.Naseera@epa.gov>
Date: August 26, 2015 at 14:26:48 EDT
To: "Alcala, Cecilia" <Alcala.Cecilia@epa.gov>, "Alexander, Laurie" <Alexander.Laurie@epa.gov>, "Avery, James" <Avery.James@epa.gov>, "Bateson, Thomas" <Bateson.Thomas@epa.gov>, "Berner, Ted" <Berner.Ted@epa.gov>, "Birchfield, Norman" <Birchfield.Norman@epa.gov>, "Bland, Naseera" <Bland.Naseera@epa.gov>, "Blessinger, Todd" <blessinger.todd@epa.gov>, "Boone-Edwards, Amanda" <Boone-Edwards.Amanda@epa.gov>, "Brinkerhoff, Chris" <Brinkerhoff.Chris@epa.gov>, "Buckley, Barbara" <Buckley.Barbara@epa.gov>, "Bussard, David" <Bussard.David@epa.gov>, "Cai, Christine" <Cai.Christine@epa.gov>, "Carmichael, Brenda" <Carmichael.Brenda@epa.gov>, "Chan, Elizabeth" <Chan.Elizabeth@epa.gov>, "Choudhury, Harlal" <choudhury.harlal@epa.gov>, "Cogliano, Vincent" <cogliano.vincent@epa.gov>, "Corona, Elizabeth" <Corona.Elizabeth@epa.gov>, "Cubbison, Christopher" <cubbison.chris@epa.gov>, "CURTIS, LUCY" <Curtis.Lucy@epa.gov>, "D'Amico, Louis" <DAmico.Louis@epa.gov>, "Deener, Kathleen" <Deener.Kathleen@epa.gov>, "Dickerson, Aisha" <Dickerson.Aisha@epa.gov>, "Euling, Susan" <Euling.Susan@epa.gov>, "Evans, Amanda" <Evans.AmandaM@epa.gov>, "Field, Malcolm" <Field.Malcolm@epa.gov>, "Flowers, Lynn" <Flowers.Lynn@epa.gov>, "Frithsen, Jeff" <Frithsen.Jeff@epa.gov>, "Fritz, Jason" <Fritz.Jason@epa.gov>, "Galizia, Audrey" <Galizia.Audrey@epa.gov>, "Gamble, Janet" <Gamble.Janet@epa.gov>, "Gatchett, Annette" <Gatchett.Annette@epa.gov>, "Gibbons, Catherine" <Gibbons.Catherine@epa.gov>, "Glenn, Barbara" <Glenn.Barbara@epa.gov>, "Grambsch, Anne" <Grambsch.Anne@epa.gov>, "Gwinn, Maureen" <gwinn.maureen@epa.gov>, "Hawkins, Belinda" <Hawkins.Belinda@epa.gov>, "Hogan, Karen" <Hogan.Karen@epa.gov>, "Hotchkiss, Andrew" <Hotchkiss.Andrew@epa.gov>, "Iuliano, Kayla" <Iuliano.Kayla@epa.gov>, "Jarabek, Annie" <Jarabek.Annie@epa.gov>, "Jinot, Jennifer" <Jinot.Jennifer@epa.gov>, "Johnson, Maureen" <Johnson.Maureen@epa.gov>, "Jones, Samantha" <Jones.Samantha@epa.gov>, "Kadry, Abdel-Razak" <Kadry.Abdel@epa.gov>, "Keshava, Nagalakshmi" <Keshava.Nagu@epa.gov>, "Kopylev, Leonid" <Kopylev.Leonid@epa.gov>, "Kraft, Andrew" <Kraft.Andrew@epa.gov>, "Lee, Janice" <Lee.JaniceS@epa.gov>, "Lin, Yu-Sheng" <Lin.Yu-Sheng@epa.gov>, "Long, Tom" <Long.Tom@epa.gov>, "Luke, April" <Luke.April@epa.gov>, "Makris, Susan" <Makris.Susan@epa.gov>, "Mehfoud, Nicholas" <Mehfoud.Nicholas@epa.gov>, "Murphy, Patricia" <Murphy.Patricia@epa.gov>, "Nath, Raghu" <Nath.Raghu@epa.gov>, "Newhouse, Kathleen" <Newhouse.Kathleen@epa.gov>, "Olden, Kenneth" <Olden.Kenneth@epa.gov>, "Owens, Beth" <Owens.Beth@epa.gov>, "Pardo, Larissa" <Pardo.Larissa@epa.gov>, "Parsons, Christy" <Parsons.Christy@epa.gov>, "Perovich, Gina" <Perovich.Gina@epa.gov>, "Persad, Amanda" <Persad.Amanda@epa.gov>, "Petersen, Dan" <Petersen.Dan@epa.gov>, "Pratt, Margaret" <pratt.margaret@epa.gov>, "Preuss, Peter" <Preuss.Peter@epa.gov>, "Reid, Jon" <Reid.Jon@epa.gov>, "Rieth, Susan" <Rieth.Susan@epa.gov>, "Ross, Christine" <Ross.Christine@epa.gov>, "Ross, Mary" <Ross.Mary@epa.gov>, "Rutigliano, Marian" <Rutigliano.Marian@epa.gov>, "Salazar, Keith"

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Subject: News Update: EPA FY16 Report Language May Be Tied To Formaldehyde Study Proposal (InsideEPA)

RISK POLICY REPORT - 08/25/2015

EPA FY16 Report Language May Be Tied To Formaldehyde Study Proposal

Posted: August 24, 2015

A proposal to test a controversial 2010 study of Chinese workers exposed to formaldehyde on the job may have spurred congressional report language attached to fiscal year 2016 EPA spending bills that call for the agency to fund an effort to replicate the study, which undergirds the conclusion in EPA's draft assessment that formaldehyde exposure can cause leukemia.

EPA's Integrated Risk Information System (IRIS) formaldehyde assessment has remained in limbo after a 2011 National Academy of Sciences (NAS) report criticized the agency's draft assessment and faulted IRIS procedures generally, prompting EPA to re-work the draft assessment largely from scratch.

The congressional report language, however, suggests that a new draft may be released next fiscal year, and again raises concerns about the controversial 2010 study that led EPA -- as well as the National Toxicology Program and the International Agency for Research on Cancer -- to conclude that exposure to formaldehyde could cause leukemia. "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," the reports from both the House and Senate appropriations committees say.

Industry has mounted an attack on the study, arguing that it has not been replicated, that its findings are unique and implausible, without a biological explanation. Several years ago, one industry source explained that while most would agree that exposure to formaldehyde could cause nasal cancer, the leukemia finding was more concerning to industries that make and use formaldehyde because of the much higher prevalence and risk associated with leukemia.

At an EPA workshop last year on formaldehyde, several speakers called for a replication of the Zhang study to definitively answer whether formaldehyde is a leukemogen.

The House Appropriations Committee appears to take up that call, directing EPA in its report 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" (*Risk Policy Report*, June 30).

An *emeritus* University of Vermont medical professor, Richard Albertini, says he presented the chemical industry association American Chemistry Council (ACC) months earlier with a proposal he says will test the Zhang study's findings. Albertini proposed developing a new cohort of formaldehyde exposed-workers, taking blood samples from them, and then submitting those samples to a test called the colony forming unit-granulocyte/macrophage (CFU-GM) assay.

The assay is used as a screen to predict the hematotoxic potential of chemicals, according to the European Centre for the Validation of Alternative Methods, which like a U.S. counterpart including EPA, validates new cellular, computational and other non-whole animal toxicity testing approaches.

In a recent interview, Albertini explains that the advantage of his approach is that it will distinguish whether any occurring aneuploidy -- too few or too may chromosomes in a cell -- arose in the workers, or occurred only after their cells were grown in petri dishes in the laboratory for the CFU-GM analysis.

"The way in which the [Zhang] study was conducted you can't tell if the aneuploidy was already present in the subjects or it came about only after the cells were out of the body and growing on the dishes," Albertini says. "If the study were done in a different way, and if the assertion that the aneuploidy actually did arise in the subjects' bodies [is correct], the distribution of the cells with aneuploidy will have a definite pattern."

Under Albertini's approach to the CFU-GM assay, when the cells taken from the workers are grown in the lab to test them, the individual colonies of the original cells would be maintained. Testing would be performed by cell colony, which would allow the researchers to determine the distribution of any aneuploid cells within and across cell colonies.
If there are colonies in which all of the cells are aneuploid, it is likely that the individual cells taken from the subjects already had the aneuploidy, Albertini explains. In this case, the chromosome changes really did arise in the bodies of the subjects.
But if the aneuploid cells are distributed in a way that a small number of them are found in all of the colonies but no colony is made up entirely of aneuploid cells, it is most likely that the aneuploidy arose in the dishes during the cells' outgrowth and the cells with aneuploidy did not originate in the workers, Albertini says.
He contrasts this approach with that used by Zhang and colleagues, who he says appear to have merged all of the cells from all of the colonies and then looked for aneuploid cells in the mixture. The result was then apparently compared to a mixture of cells from unexposed control subjects. But Albertini says it is aneuploid colonies, not cells, that is the marker of aneuploidy that arose in the body, and therefore of interest in a study to determine if formaldehyde has these chromosome effects on blood forming cells in humans.
"This cannot be determined from the study of Zhang et al," Albertini says, adding that the researchers should be congratulated for introducing the issue. "The importance of this question should push for a repeat study of formaldehyde exposed workers but performed in a manner where the important distinction between changes in the body or changes on petri dishes can be determined."

Albertini, who also attended EPA's formaldehyde workshop last year, says that researchers should stop arguing about the results of the Zhang study and their meaning, and instead, undertake the test he proposes. It would require finding a set of workers to sample, setting up a study review board which Albertini says should include Zhang or members of her team, EPA representatives and uninterested scientists to oversee the project. Further, he recommends that the CFU-GM testing be undertaken by a disinterested medical lab, such as one at the University of Cincinnati specializing in leukemia. Additionally, the analysis should be performed by uninterested, third-party statisticians, he says.

In his proposal to ACC, Albertini estimates that the study would cost around $200,000. *The proposal is available on InsideEPA.com. (Doc. ID: 184209)*
Albertini says that ACC asked EPA to fund the study, and the agency declined.
Asked to comment, an ACC spokeswoman did not respond to the question, saying only, "[w]e fully support the replication of the Zhang study and encourage the EPA to follow-through on the NAS 2011 report and the 2014 workshop recommendations that the findings must be reproduced."
An EPA spokesman did not respond to a request for comment by press time.

Zhang and colleagues at the University of California Berkeley have attempted to further investigate the findings of their earlier study with additional research. The most recent publication appeared in the journal *Carcinogenesis* in January, performing a broader chromosomal analysis to samples saved from the same workers included in the 2010 study. The study concludes that "our findings strengthen the evidence that leukemia-related aneuploidies and structural changes, especially in chromosomes 5 and 7, can arise in the myeloid progenitor cells of healthy workers exposed to [formaldehyde], and may be a potential mechanism underlying [formaldehyde]-induced leukemia."
Zhang and colleagues' newest publication -- which also employed the CFU-GM approach -- addresses Albertini's concern that the anueploidy observed in their studies could have occurred *in vitro*, rather than *in vivo*. The study acknowledges it as "a potential limitation of our study," but suggests that if so, this occurrence still supports the argument that formaldehyde exposure can cause leukemia.

"These events would therefore reflect a greater tendency for CFU-GM cells from workers exposed to [formaldehyde (FA)] to develop chromosomal abnormalities during cell growth compared to control workers who were unexposed to FA," the research team writes in the discussion section of their January publication. "Their significant association with FA exposure clearly shows the potential for FA-related genetic damage or DNA--protein crosslinks to manifest as leukemia-related chromosome changes in subsequent generations of myeloid cells arising from committed and early progenitors. Given the dynamic proliferation of stem cells and progenitor cells in human bone marrow during hematopoiesis, a greater tendency to develop chromosomal abnormalities would also support the leukemogenic potential of FA."
One of Zhang's co-authors, Martyn Smith, also a professor at Berkley, questions Albertini's approach in an email to *Risk Policy Report*. "His proposal to use a CFU-GM assay as we did, but to analyze single colonies instead of pooled ones, is interesting but would be much harder to do in practice (it is already very challenging to perform CFU-GM assays in the field) and would add little additional

information in my view," Smith writes. "The important point is that the FA exposed workers had higher levels of aneuploidy in these CFU-GM cultures compared to matched unexposed controls. Replicating this finding would be of scientific interest but is not essential to regulatory action on formaldehyde in my view."

Smith adds that the research team shared the findings of their latest publication with EPA team conducting the formaldehyde IRIS assessment. "The science is clear in my view," Smith says. "Multiple studies have shown that formaldehyde causes chromosome damage in human blood cells and it is a reproductive toxicant harming the testes. If it can reach the testes to do harm, it can reach the bone marrow to cause leukemia." -- *Maria Hegstad*

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