Message

From: Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]
Sent: 11/13/2013 5:26:45 PM
To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Bateson, Thomas [Bateson.Thomas@epa.gov]; Cooper, Glinda [Cooper.Glinda@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Jinot, Jennifer [Jinot.Jennifer@epa.gov]; Whalan, John [Whalan.John@epa.gov]; Makris, Susan [Makris.Susan@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Sonawane, Bob [Sonawane.Bob@epa.gov]; White, Paul [White.Paul@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Segal, Deborah [Segal.Deborah@epa.gov]; Fritz, Jason [Fritz.Jason@epa.gov]; Kushman, Mary [Kushman.Mary@epa.gov]
Subject: RE: TALKS TODAY ON FORMALDEHYDE & METHANOL
Attachments: RASS Webinar_11 13 13_Endogenous Approaches.ppt

Thanks Ravi for the reminder. I will be listening to the talks. Here are the slides for all the four talks in one PowerPoint file, just in case if someone want it. I see some new work done on testing artifactual generation of FA with different buffers and Tris.
Sury

Sury Vulimiri, Ph.D., DABT
National Center for Environmental Assessment, Office of Research & Development, US EPA
Phone: 919-541-3558 | Fax: 919-541-0245 | vulimiri.sury@epa.gov
USPS Address: US EPA, Research Triangle Park, NC 27711
Physical Address: US EPA, M.D. B243-01, 109 T.W. Alexander Dr, Research Triangle Park, NC 27711
UPS, FEDEX & Other Delivery Address: U.S. EPA, M.D. B243-01, 4930 Old Page Rd, Durham, NC 27703

From: Subramaniam, Ravi
Sent: Wednesday, November 13, 2013 12:08 PM
To: Bateson, Thomas; Cooper, Glinda; Glenn, Barbara; Jinot, Jennifer; Whalan, John; Makris, Susan; Subramaniam, Ravi; Vulimiri, Suryanarayana; Kraft, Andrew; Sonawane, Bob; White, Paul; Bussard, David; Segal, Deborah; Fritz, Jason; Kushman, Mary
Subject: TALKS TODAY ON FORMALDEHYDE & METHANOL

Please attend if you can. I will be unable to attend.

"Approaches to Dose-response Analysis for Compounds with Endogenous Production".
Dr. James Swenberg of the University of North Carolina at Chapel Hill and Tom Starr of TBS Associates will present on the topic by discussing formaldehyde
Drs. Jeff Gift and Paul Schlosser of the US EPA will present an approach recently applied to methanol.

From: Jarabek, Annie
Sent: Thursday, November 07, 2013 4:01 PM
To: Olden, Kenneth; Vandenberg, John; Walsh, Debra; Sams, Reeder; Burgoon, Lyle; Cogliano, Vincent; Perovich, Gina; Bussard, David; Flowers, Lynn; Chiu, Weihsueh; White, Paul; Jinot, Jennifer; Subramaniam, Ravi; Gwinn, Maureen; Sasso, Alan; Fritz, Jason; Brinkerhoff, Chris; Rieth, Susan; Gatchett, Annette; Lipscomb, John; McLanahan, Eva
Subject: FW: Risk Assessment Specialty Section (RASS) Webinar: November 13, 2013

Dear HHRA / NCEA Colleagues
I am sending this announcement again (apologies to those RASS members for those for which it is redundant) as the general topic is critical for us, and the specific examples "close to home".
Please pass it along to those scientists on your staff that may be interested in this topic. I have tried my best but likely missed many...
Thanks,
Annie

From: SOT Headquarters [mailto:SOTHQ@toxicology.org]
Sent: Thursday, November 07, 2013 1:38 PM
To: Jarabek, Annie
Subject: Risk Assessment Specialty Section (RASS) Webinar: November 13, 2013

Dear RASS Members,

Now that the government shutdown has passed, we will continue the RASS webinar series on November 13th at our standard time (3:00 EST). Please note that the presentations by Drs. Elaine Hubal and John Wambaugh previously announced for October have been rescheduled for December 11th.

Our webinar for November 13th is devoted to a topic that truly advances the current state of our science: "Approaches to Dose-response Analysis for Compounds with Endogenous

Production". Two case studies will be presented to highlight the issues. Dr. James Swenberg of the University of North Carolina at Chapel Hill and Tom Starr of TBS Associates will present on the topic by discussing formaldehyde; and Drs. Jeff Gift and Paul Schlosser of the US EPA will present an approach recently applied to methanol. We will follow these with a general discussion of issues and data needs.

Abstracts for both talks, together with some reference citations, as well as logistics on how to access the website are provided below.

The file for the presentations will be available for download on Monday November 11th in the "Downloads" section the RASS homepage. The RASS URL is as follows:
http://www.toxicology.org/ISOT/SS/RiskAssess/downloads.asp
In the event that link does not work directly in your browser, go to the SOT homepage (www.toxicology.org), choose "Members/Scientists" from the orange banner boxes across the top of the page. Then click on the "Access Specialty Sections" box on the right-hand side. From the drop-down menu of specialty sections that appear, choose "Risk Assessment". Once on the RASS homepage, click on "Downloads" (directly under the logo banner) between "Photo Gallery" and "Links".

Please join us for these exciting presentations on a very contemporary and critical topic.

Cheers,

Annie

Annie M. Jarabek

Senior Toxicologist
National Center for Environmental Assessment (NCEA)
Acting Deputy Director
Human Health Risk Assessment (HHRA)
Office of Research and Development
US EPA
Phone: 919.541.4847
Mobile (best): 919.637.6016
Email: Jarabek.annie@epa.gov

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Risk Assessment Specialty Section (RASS)
Monthly Webinar

Wednesday November 13 3:00 to 4:30 p.m. (EST)
(See below for Instructions on Webinar Access)

Approaches to Dose-response Analysis for Compounds with Endogenous Production: Two Case Studies Critical Issues for Formaldehyde Cancer Risk Assessment

James A. Swenberg, Ph.D.
Kenan Distinguished Professor
Department of Environmental Sciences and Engineering

UNC Gillings School of Global Public Health
University of North Carolina at Chapel Hill

Thomas B. Starr, Ph.D.
TBS Associates
Raleigh, NC

Abstract

Formaldehyde is a widely used chemical that is also formed endogenously in every living cell. It has been shown to induce a high incidence of squamous cell carcinomas of the nasal tissues of rats following chronic inhalation, but no carcinogenic sites distant to the nose. IARC has designated formaldehyde to be a human carcinogen, inducing leukemia and nasopharyngeal cancer based on epidemiologic studies. This webinar will focus on Mode of Action studies in rats and nonhuman primates that utilize stable isotope-labeled formaldehyde to differentiate between endogenous DNA and protein adducts and those induced by exposure. It will also present new data on the kinetics of DNA adduct formation, the fate of DNA-protein cross-links, and potential sources of artifact. The complications that arise from using inhaled formalin solution instead of formaldehyde will also be discussed, as will impacts of this information and previous modeling studies on formaldehyde risk assessment. A brief overview of the novel "bottom-up" approach to assessing low-dose cancer risks from endogenous chemicals will also be presented.

References for Formaldehyde Presentation

Lu K, Collins LB, Ru H, Bermudez E, Swenberg JA. Distribution of DNA Adducts Caused by Inhaled Formaldehyde is Consistent with Induction of Nasal Carcinoma but not Leukemia. *Toxicol Sci. 116*(2):441-51 (2010). PMCID: PMC2905397.

Lu K, Ye W, Zhou L, Collins LB, Chen X, Gold A, Ball LM, Swenberg JA. Structural characterization of formaldehyde-induced cross-links between amino acids and deoxynucleosides and their oligomers. *J Am Chem Soc. 132*(10):3388-99 (2010). PMCID: PMC2866014.

Lu K, Moeller B, Doyle-Eisele M, McDonald J, Swenberg JA. Molecular Dosimetry of N(2)-Hydroxymethyl-dG DNA Adducts in Rats Exposed to Formaldehyde. *Chem Res Toxicol. 24*(2):159-61 (2011). PMCID: PMC3128468.

Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, Starr TB. Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment. *Toxicol Sci. 120* (Suppl 1):S130-45 (2011). PMCID: PMC3043087.

Moeller BC, Lu K, Doyle-Eisele M, McDonald J, Gigliotti A, Swenberg JA. Determination of N(2)-Hydroxymethyl-dG Adducts in the Nasal Epithelium and Bone Marrow of Nonhuman Primates Following (13)CD(2)-Formaldehyde Inhalation Exposure. *Chem Res Toxicol. 24*(2):162-4 (2011). PMCID: PMC3273041.

Lu K, Gul H, Upton PB, Moeller BC, Swenberg JA. Formation of Hydroxymethyl DNA Adducts in Rats Orally Exposed to Stable Isotope Labeled Methanol. *Toxicol Sci.* 126:28-38 (2012). Epub 2011 Dec 8. PMCID: PMC3289495.

Swenberg JA, Moeller BC, Lu K, Rager JE, Fry RC, Starr TB. Formaldehyde Carcinogenicity Research: 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. *Toxicol Pathol.* 2013 Feb;41(2):181-9. Epub 2012 Nov 16.

Starr TB and Swenberg JA. A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. *Regul Toxicol Pharmacol.* 2013 Apr;65(3):311-5. Epub 2013 Jan 23. PMID: 23352840.

Rager JE, Moeller BC, Doyle-Eisele M, Kracko D, Swenberg JA, Fry RC. Formaldehyde and Epigenetic Alterations: MicroRNA Changes in the Nasal Epithelium of Nonhuman Primates. *Environ Health Perspect.* 2013 Mar;121(3):339-44. Epub 2013 Jan 14. PMCID: PMC3621188.

Edrissi, B., Taghizadeh, K. Moeller, B.C., Kracko, D., Doyle-Eisele, M., Swenberg, J.A. and Dedon, P.C. Dosimetry of N^6-formyllysine adducts following [$^{13}CD_2$]-formaldehyde exposures in rats. *Chemical Research in Toxicology.* 2013. DOI: 10.1021/tx400320u (on line)

Rui Yu, R., Moeller, B.C., Lai, Y., Doyle-Eisele, M., Kracko, D., Bodnar, W.M., Starr, T.B. and Swenberg, J.A. Kinetics of inhaled formaldehyde DNA adduct formation and loss in rats, DNA-protein cross-link breakdown, and potential for artifactual biomarker formation. (In Preparation).

Conolly, R.B., Kimbell, J.S., Janszen, D., Schlosser, P.M., Kalisak, D., Preston, J., Miller, F.J. Biologically motivated computational modeling of formaldehyde carcinogenicity in the F344 rat. *Toxicol Sci.* 2003 Oct;75(2):432-47. Epub 2003 Jul 11. PubMed PMID: 12857938.

Derivation of Methanol RfD and RfC – Accounting for Background Blood Levels

Jeffrey S. Gift, Ph.D.
National Center for Environmental Assessment
Hazardous Air Pollutants Assessment Branch
RTP, NC

Paul M. Schlosser, Ph.D.
National Center for Environmental Assessment
Integrated Risk Information System
Washington, DC

Abstract

Methanol can be formed in the mammalian organism as a metabolic byproduct. Diet can contribute to background levels of methanol, principally from the ingestion of fruits and vegetables. The recent 2013 EPA methanol assessment derives an oral reference dose (RfD) and inhalation reference concentration (RfC) that represent estimates of daily exposures to a population above endogenous background that are likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (http://epa.gov/iris/subst/0305.htm). In doing so, EPA needed to make important determinations or assumptions regarding the following:

- identifying the effects of concern;
- determining the causal toxic moiety and its most appropriate, measurable internal dose metric;
- understanding the physiologically-based pharmacokinetic (PBPK) relationships between internal doses and external doses for laboratory animals and humans;
- estimating the lowest benchmark dose increase over background that is associated with a risk level that can be reliably estimated across evaluated endpoints;
- characterizing the increase in this causal moiety in terms of an increase in internal dose over background that would not cause an appreciable human health risk;
- deriving the oral RfD and inhalation RfC based on the internal dose metric; and
- assessing relationship between the RfD/C and background methanol blood levels.

This presentation will summarize the basis for the choices EPA made with respect to these key determinations and assumptions for deriving an RfD and RfC that are believed to be without appreciable risk to a population with an existing background level of methanol.

Disclaimer: The views expressed in this paper are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

WEBINAR ACCESS INSTRUCTIONS

Event address for attendees: https://aim-hqevents.webex.com/aim-hqevents/onstage/g.php?d=664283858&t=a
Event number: 664 283 858
Event password: RASS

Teleconference information

Call-in toll-free number (US/Canada): 1-877-668-4490
Call-in toll number (US/Canada): 1-408-792-6300
Global call-in numbers: https://aim-hqevents.webex.com/aim-hqevents/globalcallin.php?serviceType=EC&ED=102416167&tollFree=1
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Access code: 664 283 858

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