Message

**From:** Ex. 6 Ex. 6
**Sent:** 3/14/2018 10:18:14 PM
**To:** Ex. 6
administrator@epa.gov; afournier@wcgrp.com; amy@rmagreen.com; aparachini@parachinigroup.com; arestuccia@politico.com; Armitage, Thomas [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=06e0b9190f534cf0b6e34da284081a14-Armitage, Tom]; ashlee.vinyard@mail.house.gov; ashley.smith@mail.house.gov; athompson@sgrlaw.com; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; beldred@analyticalservices.com; benton.donald@epa.gov; bess.larson@mail.house.gov; blaira@mail.nih.gov; Ex. 6 Bowman, Liz [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c3d4d94d3e4b4b1f80904056703ebc80-Bowman, Eli]; Ex. 6 brett.grannemann@leg.wa.gov; bryan.yon@leg.wa.gov; bryan_zumwalt@americanchemistry.com; c.portier@mastrichtuniversity.com; carolyn.mcintosh@squirepb.com; Carpenter, Thomas [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c286cf1692fa46dc9636a7c49c0925b8-Carpenter, Thomas]; Carpenter, Thomas [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c286cf1692fa46dc9636a7c49c0925b8-Carpenter, Thomas]; catherine.vanway@cummins.com; cecilia.kang@nytimes.com; chris.wydler@mail.house.gov; Ex. 6 Ex. 6 clarkg@khlaw.com; claude@masdisonlaw.com; cogaliano.vincent@epa.gov; Ex. 6 daniel.j.scavino Ex. 6
**Subject:** PROJECT

Would you be interested in a business project? Kindly contact my office for details if interested ONLY
Jennifer Ruiz

Message

**From**: Gibson, Jacqueline MacDonald [jackie.macdonald@unc.edu]
**Sent**: 2/6/2018 2:42:37 AM
**To**: Druwe, Ingrid [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5ffcfa93d12d4d92a7acd2730c889994-Druwe, Ingrid]
**CC**: drsg-l@indiana.edu; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Rick Reiss [rreiss@exponent.com]; Musso, Michael P. [Michael.Musso@hdrinc.com]; Ed Pfau [epfau@hullinc.com]; Lowney, Carrie A [carrie.a.lowney@zoetis.com]; Ian Collins [Ian.Collins@ghd.com]; Blessinger, Todd [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f5240ca690c84f8fb20bac6fd7273fd5-Blessinger, Todd]; Wayne Landis [Wayne.Landis@wwu.edu]; Dalaijamts, Chimeddulam [CDalaijamts@cvm.tamu.edu]; Barbara D. Beck [BBECK@gradientcorp.com]; Lorenz Rhomberg [lrhomberg@gradientcorp.com]; Mary Jane Calvey [mjcalvey@rwmsinc.com]; Woodall, George [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a617aad87171414a8b9fca5ce395a899-Woodall, George]; Haas,Charles [haas@drexel.edu]; Setzer, Woodrow [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=290e3e834a3c4269a441c13712fffc0c-Setzer, Rhyne]; Wout Slob [wout.slob@rivm.nl]; Chiu, Weihsueh [WChiu@cvm.tamu.edu]; Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; Jarabek, Annie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8b1de54d48e1429c8129f6499211dbdb-Jarabek, Annie]; Berner, Ted [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f1949c9653024d3cb4aa4c2bd69c4fde-Berner, Ted]; Bette Meek [bmeek@uottawa.ca]; Gibson, Jacqueline MacDonald [jackie.macdonald@unc.edu]; Philip Goodrum [pgoodrum@integral-corp.com]; Robby and Brandolyn Thran[ Ex. 6 ]; Kenneth Bogen [kbogen@exponent.com]; xly@bnu.edu.cn; Arno Swart [arno.swart@rivm.nl]; Yeager, Raymond (Phil) [Raymond.Yeager@fda.hhs.gov]; riesd@michigan.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a989ecdcc6514a5fb11354a2f94aa001-riesd@michigan.gov]; Robinan Gentry [rgentry@ramboll.com]; Petersen, Dan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05e14a620a164436adfae701533b4cd5-Petersen, Dan]; Zemin Wang [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ea9552e19af64d3c9f1c06cf415be822-Zemin Wang]; Scarano, Louis [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=298e8a818eb6426bb5731a202ab1ac17-Scarano, Louis]; Bussard, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf26b876393e44f38bdd06db02dbbfe5-Bussard, David]; Evans, John S. [jevans@hsph.harvard.edu]; Putzrath, Resha M CIV USN NAVMCPUBHLTHCEN PORS (US) [resha.m.putzrath.civ@mail.mil]; Wright, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0087b3fe163145869deead8b626fbfa3-Wright, Michael]; Kopylev, Leonid [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=abfe6798809e4c8c8a27452ec86726d8-Kopylev, Leonid]; Swartout, Jeffrey [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4630fcf74e684ca4b9ffff43715fd031-Swartout, Jeffrey]; Young, Melanie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=68e2dfcf2de44532a6fc488358383008-Young, Melanie]; Janet Kester [jkester@newfields.com]; Farrar, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=edef06d4c2984c0ca28018de77009f4f-Farrar, David]; Simmons, Jane [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4fd75018b00b4fc29134386374395f44-Simmons, Jane]; Gift, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=746b029cd80e437d9f62708c339a9ec8-Gift, Jeff]; Theodore, Shaji [Shaji.Theodore@fda.hhs.gov]; Rick_Becker@americanchemistry.com [/o=ExchangeLabs/ou=Exchange

Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f03aaee7f1014aad916f86c53f886717-Rick_Becker@americanchemistry.com]

**Subject:** Re: Reminder: DRSG Monthly Meeting Today

Hi All,

I have on my calendar that we have our monthly meeting tomorrow. Unfortunately, I've been called to an 11:45-12:45 by folks above my pay grade, and I can't miss this one. I'll try calling in after my meeting to check in.

Please accept my apologies.

Jackie

Dr. Jacqueline MacDonald Gibson
RTI University Scholar, 2017-2018
Associate Professor, Department of Environmental Sciences and Engineering
Gillings School of Global Public Health
University of North Carolina, Chapel Hill
Michael Hooker Research Center 0032
Campus Box 7431
Chapel Hill, NC 27599-7431
jackie.macdonald@unc.edu
Phone: 919-966-7892
Fax: 919-966-7911
http://www.unc.edu/~macdonaj/

On Jan 9, 2018, at 12:09 PM, Druwe, Ingrid wrote:

Proposed ideas for symposia:

- Dose Response and Law
- Success of DR
- Systematic review and DR
- Machine Learning & SR-Translate science to decision (jackie volunteered for this one)
- New data for use in DR; how to communicate data → Segway to symposia
- Attention to how to properly design experiments to inform DR
- Scott Auerbach- BMD Express-NIH version
- How to facilitate open data dose response health benefits- Dan Kruskie of Iowa (CatReg?); Neal Fann OAQPS BenMap

Moving meeting to 2nd Tuesday in January to accommodate travel & holiday schedules. Please make note of new Adobe connect & web conferencing information
Call-in number(s) and access code(s)
Teleconference: **Ex. 6**
Adobe Connect: https://epawebconferencing.acms.com/drsg/

Message

**From**: Morris, Jeff [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=55C34872E6EA40CAB78BE910AEC63321-MORRIS, JEFF]
**Sent**: 7/30/2018 11:38:50 AM
**To**: Thomas, Karluss [Karluss_Thomas@americanchemistry.com]
**CC**: Blair, Susanna [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6c869b985f3d43db982c18aaabd826bd-Blair, Susa]; Grant, Brian [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ec6104b72cab42ba9b1e1da67d4288ae-Grant, Brian]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bertrand, Charlotte [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f044d768e05842e1b75321ff6010e1b8-Bertrand, Charlotte]; Baptist, Erik [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=10fc1b085ee14c6cb61db378356a1eb9-Baptist, Er]; Pierce, Alison [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=036313052e20472ca55f7733de62f969-APierce]; Vendinello, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3951cb8019444df48b4d969cdf56f188-Lvendi02]; Fehrenbacher, Cathy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=369151285d0143bba4f6fb3f9991e583-CFehrenb]; Hartman, Mark [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7eeb1ab7c7a74b40bf9bfded67e7fafd-Mark A Hartman]
**Subject**: Response to March 28 Letter
**Attachments**: Response D4 26 July 2018.pdf

Dear Karluss,

Attached is the EPA's response to your March 28, 2018 letter regarding D4. We also will send you the original via regular mail.

All the best,

Jeff

Jeffery T. Morris, PhD
Director, Office of Pollution Prevention & Toxics
US Environmental Protection Agency

1200 Pennsylvania Avenue, NW (MC-7401M)
Washington, DC 20460

(202) 564-3810

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 26, 2018

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Karluss Thomas
American Chemistry Council
Silicones Environmental Health, and Safety Center

Dear Mr. Thomas,

Thank you for your March 28, 2018 letter regarding the completion of a risk evaluation for Octamethylcyclotetrasiloxane (D4).

Under amended TSCA, EPA is now directed to evaluate existing chemicals for unreasonable risk of injury to health or the environment. The law mandates the process by which EPA must evaluate existing chemicals, and the timelines for which these actions must be completed. The first step is a 9- to 12-month prioritization process involving risk-based screening of hazard and exposure potential to determine if the chemical is high- or low-priority for risk evaluation. If the chemical is designated as high-priority, it moves directly into risk evaluation, where within three and a half years, EPA must determine if the chemical presents an unreasonable risk of injury to health or the environment under the conditions of use. By statute, EPA must have 20 high-priority risk evaluations ongoing by December 2019; therefore, EPA plans to begin prioritization between December 2018 and March 2019. EPA is in the process of determining how chemicals will be selected for prioritization. If D4 were to be one of the first chemicals selected for prioritization, and if it were determined to be a high-priority chemical, a risk evaluation would be completed no later than June 2023.

An alternative route for a chemical to be evaluated for risk is the TSCA provision under which manufacturers may request that a chemical they manufacture undergo an EPA-conducted risk evaluation. The final risk evaluation rule (Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 82 FR 33726, June 22, 2017), defines the form and manner under which these requests must be made to the Agency, along with EPA's process to accept a request and begin the risk evaluation. If a request is granted, the Agency will begin the risk evaluation, which must be completed within three and a half years. This method bypasses the 9- to 12-month prioritization process. Note that EPA will not initiate a manufacturer requested risk evaluation until the finalization of the fees rule.

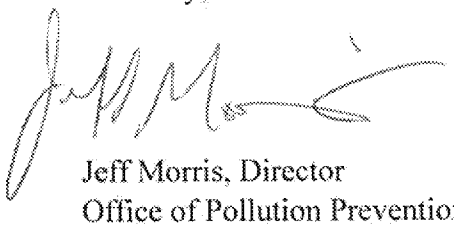
Additionally, you could provide a draft risk evaluation with, or without, a manufacturer request for risk evaluation. On June 22, 2017 EPA published guidance to assist interested persons in developing and submitting a draft risk evaluation. EPA would consider this draft risk

evaluation as reasonably available information to be considered, along with other information, in an EPA-conducted risk evaluation.

You cite TSCA section 26(p)(2), which allows the Agency to initiate, continue, or complete a risk evaluation prior to the completion of policies, procedures and guidance required, as a mechanism by which a risk evaluation on D4 could be expedited. You note that 40 CFR 702.35 states that risk evaluations initiated prior to the effective date of the rule will be conducted in accordance with the rule to the maximum extent practicable. However, although EPA has received information through implementation of the enforceable consent agreement, OCSPP has not initiated a D4 risk assessment.

Thank you for your letter.

Sincerely,



Jeff Morris, Director
Office of Pollution Prevention and Toxics

Message

**From**: Clare Thorp [cthorp@bio.org]
**Sent**: 1/11/2018 9:41:09 PM
**To**: Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC**: Clare Thorp [cthorp@bio.org]
**Subject**: Would you mind giving some more time for comments on Section 5 please?
**Attachments**: BIO request for extension to the comment period on the New Chemicals Review program implementation.pdf

**Importance**: High

Hi Jeff, Nancy
Hope you are well and wishing you a Happy New Year.

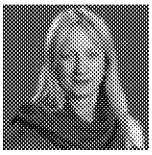
This email is to provide you with a heads up for a letter from BIO which we have just posted to the docket, requesting a 30 day extension to the comment period for the New Chemicals Review program, specifically to documents :
1. Draft Points to Consider when preparing new chemical notifications and
2. New chemicals decisions manual

I'm sending it to you directly because time is of the essence, as these comments are due on Jan 20th and we only received copies of these documents at the December 6th meeting. I know it can take some time to post things to the docket and so I'm trying to minimize possible delays associated with this (if I'm wrong, I'd be glad to know!).

That said, BIO is doing our best to meet the comment deadline, but a bit more time would be very helpful towards providing you with meaningful stakeholder feedback.

Sincerely
Clare Thorp

**Clare Thorp, Ph.D.**
Managing Director, Industrial and Environmental
Biotechnology Innovation Organization
cthorp@bio.org
Ph. Ex. 6 (direct)
www.bio.org



Biotechnology Innovation Organization

25 YEARS OF INNOVATION

January 11, 2018

Nancy B. Beck
Deputy Assistant Administrator, Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Re: Docket ID No. EPA-HQ-OPPT-2017-0585

Dear Deputy Assistant Administrator Beck:

The Biotechnology Innovation Organization (BIO)'s Industrial and Environmental Section (IES) respectfully requests a 30-day extension to the comment period for the U.S. Environmental Protection Agency (EPA or the Agency)'s New Chemicals Review Program Implementation under the Toxic Substances Control Act as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (TSCA), currently ending on January 20, 2018. An extension until February 19, 2018, is needed to allow stakeholders sufficient time to consider the new material provided by the Agency on December 6, and to organize meaningful comments and feedback.

BIO IES represents the companies which manufacture biobased or 'renewable' chemicals using biotechnology. Many are small to medium sized and the New Chemicals Program is the route by which their products are regulated prior to their release onto the market. Any changes to the current system of reviewing new chemicals will, therefore, have a significant impact on the decision making and resource requirements of our members. Because of this, the documents and presentation provided by the Agency on December 6, 2017, are of great importance to BIO members and they would like to ensure they have ample opportunity to provide an adequate and helpful response to the Agency. A 30-day extension would provide the necessary time to process, review, and comment on these technically complex documents, particularly as this is one of three comment deadlines for separate and distinct TSCA implementation initiatives, all of which are in the formative stage. Namely, comments on EPA's Strategic Plan for Alternative Test Methods were due January 10, these comments are due by January 20, and comments on EPA's proposed Approaches for Prioritization are due by January 25. In the case of the Alternative Testing comment submission deadline, EPA did allow an extension of time which was helpful albeit rather short.

Furthermore, it is unclear whether there will be a future opportunity to comment on the new material or the proposed changes to the program before they are finalized. If this is stakeholders' opportunity to engage the Agency, it is important that the Agency ensure this opportunity to comment is sufficient to gain meaningful feedback from the regulated community.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 »
202.488.6301 »
bio.org

**Importance of New Information and Need for an Extension:**

On December 6, 2017, EPA held a public stakeholder meeting to update and engage with the public on the Agency's progress in implementing changes to the New Chemicals Review Program as a result of the 2016 amendments to TSCA, including discussion of EPA's draft New Chemicals Decision-Making Framework. At this meeting, EPA described its review process for new chemical substances under the amended statute and allowed interested parties to provide input and to ask questions. The Agency plans to utilize the feedback it receives from the public meeting and comments received to improve policy and processes relating to the review of new chemicals under TSCA.

During the stakeholder meeting EPA provided two new documents to stakeholders for review and comment. It should be noted that this was the first time these documents had been provided to the public with explanation and for comment. They are:

1. Draft Points to Consider when preparing new chemical notifications

2. New chemicals decisions manual

Upon conclusion of its presentation of these materials, EPA requested input from stakeholders on a number of important items. The following is a nonexclusive list of items that that the Agency raised, that are of importance to BIO members and for which additional time is needed to adequately address.

- The use of Significant New Use Rules, particularly as this can extend the review period by up to 180 days;
- Whether EPA should consider exposure in its determinations of "not likely to represent a risk" – currently the only chemicals which have obtained this determination are of low hazard (EPA followed up on this request and the response was posted on January 8, 2018);
- How far into the future is "reasonably foreseeable", and how will the Agency define this term, plus the uncertainty the further into the future one projects;
- Implementation of a pre-notice consultation process, which encourages companies to consult with EPA prior to submitting a Premanufacture Notice so that companies know what information they will be required to provide;
- Whether low solubility Class 2 chemicals need appropriate test methodologies;
- EPA stated that companies need to pay attention to the default assumptions that will be made in the absence of information. They are very conservative. For example, in the absence of data on particle size distribution, EPA will assume the particles are respirable. During the public meeting, interest was expressed by the regulated community in receiving more information on how the scores for EFATE are determined and how ECOSAR data are used.

- The current status of the Sustainable Futures program – whether it is still relevant, should it be updated, do they need to increase or decrease the number of training workshops, should they update the framework manual to reflect TSCA as amended.

Providing responses to these more specific requests is important and necessary, but will require time for industry associations to consult with their members.

We thank the Agency for providing this opportunity to engage with it, for developing comprehensive written material and for providing the forum at which this material was presented. BIO members recognize the significant time and resources the Agency has invested in doing so. To provide meaningful feedback to the Agency, we request that the timeline for receiving comment be extended by a minimum of 30 days to ensure members have the time needed to provide a substantive response to this significant endeavor by the EPA, one which impacts our members considerably, both now and into the future.

Sincerely,

Clare Thorp, PhD
Managing Director, Industrial and Environmental Section
Biotechnology Innovation Organization

Message

**From**: Morris, Jeff [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=55C34872E6EA40CAB78BE910AEC63321-MORRIS, JEFF]
**Sent**: 1/12/2018 3:09:41 PM
**To**: Clare Thorp [cthorp@bio.org]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC**: Scheifele, Hans [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dd4c2e03967741c2a8d643869c0681db-HScheife]
**Subject**: RE: Would you mind giving some more time for comments on Section 5 please?

Hi Clare. Nice to hear from you. Happy 2018 to you too!

If you're not able to get comments in by the 20th, please just send them directly to Hans, copying me, when you can and we will ensure that they get in the docket. This will be more efficient than going through the process steps of formally extending the comment period.

All the best,

Jeff

Jeffery T. Morris, PhD
Director, Office of Pollution Prevention & Toxics
US Environmental Protection Agency

1200 Pennsylvania Avenue, NW (MC-7401M)
Washington, DC 20460

(202) 564-3810

**From:** Clare Thorp [mailto:cthorp@bio.org]
**Sent:** Thursday, January 11, 2018 4:41 PM
**To:** Morris, Jeff <Morris.Jeff@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
**Cc:** Clare Thorp <cthorp@bio.org>
**Subject:** Would you mind giving some more time for comments on Section 5 please?
**Importance:** High

Hi Jeff, Nancy
Hope you are well and wishing you a Happy New Year.

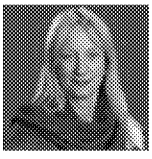
This email is to provide you with a heads up for a letter from BIO which we have just posted to the docket, requesting a 30 day extension to the comment period for the New Chemicals Review program, specifically to documents :
1. Draft Points to Consider when preparing new chemical notifications and
2. New chemicals decisions manual

I'm sending it to you directly because time is of the essence, as these comments are due on Jan 20th and we only received copies of these documents at the December 6th meeting. I know it can take some time to post things to the docket and so I'm trying to minimize possible delays associated with this (if I'm wrong, I'd be glad to know!).

That said, BIO is doing our best to meet the comment deadline, but a bit more time would be very helpful towards providing you with meaningful stakeholder feedback.

Sincerely
Clare Thorp

**Clare Thorp, Ph.D.**
Managing Director, Industrial and Environmental
Biotechnology Innovation Organization
cthorp@bio.org
Ph. Ex. 6 (direct)
www.bio.org



Message

**From**: Gibson, Jacqueline MacDonald [jackie.macdonald@unc.edu]
**Sent**: 1/9/2018 5:21:37 PM
**To**: Druwe, Ingrid [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5ffcfa93d12d4d92a7acd2730c889994-Druwe, Ingrid]
**CC**: drsg-l@indiana.edu; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Rick Reiss [rreiss@exponent.com]; Musso, Michael P. [Michael.Musso@hdrinc.com]; Ed Pfau [epfau@hullinc.com]; Lowney, Carrie A [carrie.a.lowney@zoetis.com]; Ian Collins [Ian.Collins@ghd.com]; Blessinger, Todd [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f5240ca690c84f8fb20bac6fd7273fd5-Blessinger, Todd]; Wayne Landis [Wayne.Landis@wwu.edu]; Dalaijamts, Chimeddulam [CDalaijamts@cvm.tamu.edu]; Barbara D. Beck [BBECK@gradientcorp.com]; Lorenz Rhomberg [lrhomberg@gradientcorp.com]; Mary Jane Calvey [mjcalvey@rwmsinc.com]; Woodall, George [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a617aad87171414a8b9fca5ce395a899-Woodall, George]; Charles Haas [haas@drexel.edu]; Setzer, Woodrow [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=290e3e834a3c4269a441c13712fffc0c-Setzer, Rhyne]; Wout Slob [wout.slob@rivm.nl]; Chiu, Weihsueh [WChiu@cvm.tamu.edu]; Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; Jarabek, Annie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8b1de54d48e1429c8129f6499211dbdb-Jarabek, Annie]; Berner, Ted [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f1949c9653024d3cb4aa4c2bd69c4fde-Berner, Ted]; Bette Meek [bmeek@uottawa.ca]; Gibson, Jacqueline MacDonald [jackie.macdonald@unc.edu]; Philip Goodrum [pgoodrum@integral-corp.com]; Robby and Brandolyn Thran[Ex. 6]; Kenneth Bogen [kbogen@exponent.com]; xly@bnu.edu.cn; Arno Swart [arno.swart@rivm.nl]; Yeager, Raymond (Phil) [Raymond.Yeager@fda.hhs.gov]; riesd@michigan.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a989ecdcc6514a5fb11354a2f94aa001-riesd@michigan.gov]; Robinan Gentry [rgentry@ramboll.com]; Petersen, Dan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05e14a620a164436adfae701533b4cd5-Petersen, Dan]; Zemin Wang [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ea9552e19af64d3c9f1c06cf415be822-Zemin Wang]; Scarano, Louis [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=298e8a818eb6426bb5731a202ab1ac17-Scarano, Louis]; Bussard, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf26b876393e44f38bdd06db02dbbfe5-Bussard, David]; Evans, John S. [jevans@hsph.harvard.edu]; Putzrath, Resha M CIV USN NAVMCPUBHLTHCEN PORS (US) [resha.m.putzrath.civ@mail.mil]; Wright, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0087b3fe163145869deead8b626fbfa3-Wright, Michael]; Kopylev, Leonid [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=abfe6798809e4c8c8a27452ec86726d8-Kopylev, Leonid]; Swartout, Jeffrey [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4630fcf74e684ca4b9ffff43715fd031-Swartout, Jeffrey]; Young, Melanie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=68e2dfcf2de44532a6fc488358383008-Young, Melanie]; Janet Kester [jkester@newfields.com]; Farrar, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=edef06d4c2984c0ca28018de77009f4f-Farrar, David]; Simmons, Jane [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4fd75018b00b4fc29134386374395f44-Simmons, Jane]; Gift, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=746b029cd80e437d9f62708c339a9ec8-Gift, Jeff]; Theodore, Shaji [Shaji.Theodore@fda.hhs.gov]; Rick_Becker@americanchemistry.com [/o=ExchangeLabs/ou=Exchange

Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f03aaee7f1014aad916f86c53f886717-Rick_Becker@americanchemistry.com]
**Subject:** Paper: characterizing interspecies uncertainty
**Attachments:** 3-2 Characterizing Interspecies Uncertainty.pdf

Dr. Jacqueline MacDonald Gibson
RTI University Scholar, 2017-2018
Associate Professor, Department of Environmental Sciences and Engineering
Gillings School of Global Public Health
University of North Carolina, Chapel Hill
Michael Hooker Research Center 0032
Campus Box 7431
Chapel Hill, NC 27599-7431
UNC e-mail: jackie.macdonald@unc.edu (preferred)
RTI e-mail: jmgibson.contractor@rti.org
UNC phone: 919-966-7892
RTI phone (preferred for 2017-2018 academic year): 919-990-8358
UNC fax: 919-966-7911
http://www.unc.edu/~macdonaj/

On Jan 9, 2018, at 12:09 PM, Druwe, Ingrid <Druwe.Ingrid@epa.gov> wrote:

Proposed ideas for symposia:

- Dose Response and Law
- Success of DR
- Systematic review and DR
- Machine Learning & SR-Translate science to decision (jackie volunteered for this one)
- New data for use in DR; how to communicate data → Segway to symposia
- Attention to how to properly design experiments to inform DR
- Scott Auerbach- BMD Express-NIH version
- How to facilitate open data dose response health benefits- Dan Kruskie of Iowa (CatReg?); Neal Fann OAQPS BenMap

Moving meeting to 2nd Tuesday in January to accommodate travel & holiday schedules. Please make note of new Adobe connect & web conferencing information
Call-in number(s) and access code(s)
Teleconference: Ex. 6 Code Ex. 6
Adobe Connect: https://epawebconferencing.acms.com/drsg/

Toxicology and Applied Pharmacology 233 (2008) 64–70

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

# Characterizing interspecies uncertainty using data from studies of anti-neoplastic agents in animals and humans

Paul S. Price [a,*], Russell E. Keenan [b], Jeffrey C. Swartout [c]

[a] The Dow Chemical Company, Toxicology & Environmental Research & Consulting, 1803 Building, Midland MI 48674, USA
[b] AMEC Earth and Environmental, 15 Franklin Street, Portland, ME 04101, USA
[c] National Center for Environmental Assessment U.S. Environmental Protection Agency, 26 W. M. L. King Drive, Cincinnati, OH 45268, USA

ARTICLE INFO

*Article history:*
Available online 16 April 2008

*Keywords:*
Uncertainty factors
Interspecies
Reference dose
Risk characterization

ABSTRACT

For most chemicals, the Reference Dose (RfD) is based on data from animal testing. The uncertainty introduced by the use of animal models has been termed interspecies uncertainty. The magnitude of the differences between the toxicity of a chemical in humans and test animals and its uncertainty can be investigated by evaluating the inter-chemical variation in the ratios of the doses associated with similar toxicological endpoints in test animals and humans. This study performs such an evaluation on a data set of 64 anti-neoplastic drugs. The data set provides matched responses in humans and four species of test animals: mice, rats, monkeys, and dogs. While the data have a number of limitations, the data show that when the drugs are evaluated on a body weight basis: 1) toxicity generally increases with a species' body weight; however, humans are not always more sensitive than test animals; 2) the animal to human dose ratios were less than 10 for most, but not all, drugs; 3) the current practice of using data from multiple species when setting RfDs lowers the probability of having a large value for the ratio. These findings provide insight into inter-chemical variation in animal to human extrapolations and suggest the need for additional collection and analysis of matched toxicity data in humans and test animals.



## Introduction

Regulatory agencies evaluate the safety of chemicals with respect to noncarcinogenic health effects by comparing either modeled or measured doses received as a result of exposure to doses believed to be "protective" of both the general population and sensitive individuals. These estimates of "protective" doses, most often expressed in units of milligram of chemical per kilogram body weight per day of exposure (mg/kg-day), include the US EPA's Reference Dose (RfD) (USEPA, 1988) and the Agency for Toxic Substances and Disease Registry's (ATSDR's) Minimum Risk Level (MRL; ATSDR, 1996). Other metrics include the European Union's Tolerable Daily Intake (TDI; EFSA, 2007), and Derived No Effect Levels (DNELs; European Union, 2007). While differing in certain details, these metrics have a common basis in their derivation, in that when human data are not available, they rely on test-animal toxicology studies. They are established by taking the dose associated with a specific toxicological endpoint and dividing the dose by a series of uncertainty factors.

One of these factors is the interspecies uncertainty factor which in the U.S. is typically assigned a value of 10. This factor addresses the fact that test animals may have higher tolerances to chemicals than humans and that the magnitude of the difference is likely to vary with the test species and the chemical. The value of 10 is based on the assumption that humans are unlikely to be 10 times more sensitive to a chemical than a test species when the doses are expressed on a mg of chemical per kg of body weight basis (Dourson and Stara, 1983).

In the last twelve years, a number of researchers have represented the uncertainty in noncancer risk assessment using probabilistic models (Baird et al., 1996; Swartout et al., 1998; Slob and Pieters, 1997, 1998; Vermeire et al., 1999, 2001; Kalberlah et al., 2003; Kodell and Chen, 2007), integrating this information into estimates of uncertainty and variation in risk findings (Price et al., 1997; Carlson-Lynch et al., 1999; Bosgra et al., 2005; Van der Voet and Slob, 2007). Such an approach requires a probability distribution that describes the uncertainty in the difference in toxicity between the test animal and humans for a given chemical. A number of researchers (Weil and McCollister, 1963; Weil, 1972; Dourson, 1994; Nair et al., 1995; Nauman and Weideman, 1995; Nessel et al., 1995) have suggested that this uncertainty might be characterized based on the inter-chemical variation in the ratio of similar toxicity endpoints in humans and animals.

Other researchers have proposed more detailed conceptual frameworks for defining this distribution. The approach in Price et al. (1997, 1999) and Swartout et al. (1998) defines the distribution in terms of the ratio of No Observed Adverse Effects Levels (NOAELs). Baird et al. (1996), Slob and Peiters (1997, 1998), and Evans et al. (2001) define the uncertainty distribution based on the ratios of $ED_{50}$s for the critical effects. Frameworks aslo differ on the issue of the existence or non existence of thresholds (Price et al., 1997, Evans et al., 2001).

* Corresponding author. Fax: +1 989 638 2425.
*E-mail address:* pprice@dow.com (P.S. Price).

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doi:10.1016/j.taap.2008.03.026

A number of studies have focused on the empirical characterization of differences in noncancer responses across species of test animals (Rhomberg and Wolff, 1998; Kalberlah et al., 2002; Schneider et al., 2004; Bokkers and Slob, 2007). In addition, differences between test animals and humans have been defined based on physiological and toxicokinetic considerations (Dourson and Stara, 1983; Andersen et al., 1995) and in terms of consistency with historical regulatory policies (Slob and Pieters, 1997, 1998; Swartout et al., 1998; Evans et al., 2001).

In this paper, we present an analysis of a toxicity data set for anti-neoplastic agents in test animals and humans. The data consist of a series of toxicological endpoints that can be considered roughly equivalent to an acute maximum tolerated dose (MTD). These data are used to calculate ratios of the MTD in humans and test animals (toxicity ratios). Using these ratios we investigate the inter-chemical variation in the differences between humans and test animals, the effect of different test animals, the impact of sample size, and the impact of having test data in multiple species.

We then discuss the relevance of these distributions for the extrapolation of toxicity measurements from test animals to humans, required probabilistic models of noncancer risks. As part of this discussion, consideration is given to the limitations of the data set and concerns raised by Brand et al. (1999, 2001) on the use of ratios of empirically measured toxicological endpoints.

## The anti-neoplastic agent data set

Anti-neoplastic agents are used in chemotherapy to preferentially destroy cancerous cells. Because differences in the relative toxicity to normal and cancerous cells for such agents may be small, chemotherapy protocols often call for administration of anti-neoplastic agents at levels that are close to doses that cause significant toxicity in humans. As part of the development of such agents, the National Cancer Institute (NCI) determines the maximum tolerated dose in humans ($MTD_H$) in short-term studies (typically 5 days). The $MTD_H$ is defined as the dose level at which no more than one of six cancer patients experience dose limiting toxicity with the next higher dose group of six patients having two or more patients experiencing dose limiting toxicity (Storer, 1989).

During developmental trials for anti-neoplastic agents, the NCI estimates the $MTD_H$ based on the results of a progressive series of acute, subacute, and subchronic toxicological studies in a battery of animal tests. This work results in toxicological data in a number of animal species. Toxicity in animals is determined differently for different species:

- $LD_{10}$ Typically derived for mice and rats. The acute (single) dose resulting in the death of 10% of a population of test animals.
- TDL (Toxic Dose Low) Typically derived for dogs and monkeys. The lowest dose that produces pathological alterations in hematological, chemical, clinical, or morphological endpoints. Doubling the TDL produces no lethality.
- $MTD_A$ The highest dose in test animals that suppresses body weight by no more than 10% in a 90-day subchronic study.

Source (Grieshaber and Marsoni, 1986).

The data for this study were taken from six articles, which were identified as containing data on the toxicity of agents in patients and in one or more test animals (Freireich et al., 1966; Goldsmith et al., 1975; Schein et al., 1979; Rozensweig et al., 1981; Grieshaber and Marsoni, 1986; Travis and White, 1988; Paxton et al., 1990). Only data on compounds administered by intravenous or intraperitoneal routes were included in the data set. For the majority of compounds the route of administration was consistent across test animals and humans. When necessary, data were normalized to a 5-day dosing regime (Freireich et al., 1966; Travis and White, 1988). This dose was estimated by summing the total dose administered to the animals over the course of the testing and dividing by five. Finally, where doses were reported in units of mass per surface area $mg/m^2$, the doses were converted to mg/kg based on standard estimates of the surface area and body weights of the relevant species (Freireich et al., 1966; Travis and White, 1988).

A total of 61 compounds animal to human was identified with data in humans and in one or more species of test animals. There were 161 animal to human ratios in total, with the number of ratios varying by species and ranging from 56 for the dog to 19 for the rat. The adjusted toxicity data from these six studies are presented in Table 1.

## Relevance of the data set to probabilistic noncancer risk assessments

While the unique nature of these data (matched human and animal toxicity data) make this data set highly relevant to the investigation of noncancer risk assessments, there are several significant limitations in the use of the data on anti-neoplastic agents. The following is a description of some of these limitations and the ways that they could cause the distribution of MTD ratios to differ from measures of human and animal thresholds required by probabilistic models.

1. *The MTD differs from NOAELs (and benchmark doses) used in the derivation of RfDs.* The MTD is a dose that is likely to be associated with some level of effects and is not equivalent to a NOAEL. Indeed, it may be greater than the Lowest Observed Adverse Effect Level (LOAEL). If the dose–response curves in humans and animals diverge at lower doses, the ratios at the different effect levels will differ. As they are not in the lower dose range, distributions of MTDs may be more similar to those based on ED50s used in the approaches suggested by Baird et al. 1996), Slob and Peiters (1997, 1998), and Evans et al. (2001).
2. *The data are drawn from short-term studies, while RfDs generally address chronic effects.* It is generally considered that chronic effects occur at lower doses than acute effects. However, it is not clear that the ratios of acute doses across species will be higher or lower than ratios of chronic doses. Thus, there is no a priori reason to suspect that the ratios of MTDs and chronic thresholds will have different median values. Differences in the variation between the two distributions might be expected to occur because there are more ways that chronic doses could differ across species than acute doses (such as differences in repair functions or in excretion rates). These factors could result in greater total variance in the distributions of dose ratios for chronic doses than for acute doses.
3. *The toxicological endpoints in the various studies vary with species and can vary across compounds.* The MTD database is composed of the results of studies performed using different study designs, protocols, and endpoints. Thus, there is uncertainty as to whether the differences in the toxicity ratios are due to the species' responses or to differences in the endpoints examined. Specific concerns include the use of acute (single) doses, the comparability of doses that cause lethality to doses that cause low level toxicity or weight change, and the differences in the levels of lethality allowed (Rhomberg and Wolff, 1998; Rhomberg and Lewandowski, 2004c). However, it should be noted that these toxicity benchmarks in humans and test animals have historically been considered comparable to doses that cause frank effects, but with a limited potential for lethality (Goldsmith et al., 1975; Grieshaber and Marsoni, 1986; Travis and White, 1988).
4. *The compounds were administered via injection to both humans and test animals and therefore do not reflect certain aspects of interspecies variation.* Absorption from the GI tract and initial metabolism in the liver will not be reflected in the data, potentially biasing the toxic dose low, particularly for direct-acting agents that undergo detoxification in the liver. Because of the absence of these factors, the variance of MTDs is expected to be less than the variance in NOAELs from oral studies.

**Table 1**
Data on the toxicity[a] of select anti-neoplastic agents

| Source and chemical | Toxic dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | Human | Mouse | Rat | Monkey | Dog |
| Freireich et al., 1966[b] | | | | | |
| Amethopterin | 0.41 | 3.2 | 0.58 | 3.0 | 0.12 |
| 6-Mercaptopurine | 27 | 86 | 51 | 56 | 14 |
| 5-Flourouracil | 15 | 42 | 25 | 18 | 10 |
| 5-Fluoro-2′-deoxyuridine | 30 | 160 | 89 | 60 | 40 |
| Nitrogen mustard | 0.20 | 1.2 | 0.37 | 0.20 | 0.48 |
| Nitromin | 2.0 | 45 | 7 | 4.8 | 4.4 |
| L-Phenylalanine mustard | 0.20 | 5.1 | 2.3 | 0.55 | 0.63 |
| Alaninemustard | 0.90 | 6.3 | | 1.5 | 1.5 |
| Cytoxan | 10 | 93 | 12 | 52 | 12 |
| ThioTEPA | 0.20 | 5.7 | 2.7 | 1.0 | 1 |
| Myleran | 0.64 | 15 | 3.7 | 6.0 | 5.8 |
| Actinomcycin D | 0.02 | 0.07 | 0.09 | | 0.03 |
| Mitomycin C | 0.20 | 2.3 | 1.3 | 0.64 | |
| Vinblastin | 0.08 | 0.6 | | | |
| Vinchristine | 0.024 | 0.18 | | | |
| Methyl GAG | 11 | 59.00 | | | |
| Schein et al., 1979; Travis and White, 1988[b] | | | | | |
| Mithramycin | 0.025 | 0.16 | | 0.12 | 0.12 |
| 9H-purine,6-(methylthio)-9-B-D-ribofuranosyl-,dehydrate | 5.0 | 46 | 8.0 | 11 | 8.0 |
| Imidazole mustard | 10 | 230 | | 170 | 14 |
| Ammonium, trimethylpurin-6-yl-chloride | 42 | 150 | | 170 | 45 |
| Pactamycin | 0.45 | 3.1 | | 0.09 | 0.11 |
| Glycinen-(diazoacetyl)-,hydra-zide | 160 | 400 | | 96 | 48 |
| Tylocrebrine | 1.9 | 19 | | 1.2 | 0.60 |
| Acetophenone | 550 | 700 | | 1500 | 490 |
| Cytosine, 1-B-d,arabinofurano-syl, monohydrochloride | 7.0 | 130 | | 36 | 18 |
| Hydrazine, 1-acetyl-2-picolinoyl | 30 | 87 | 61 | 120 | 58 |
| Phosphorodiamidic acid, *N,N*,-bis (2-chloroethyl), with cyclohexylamine (1:1) | 2.7 | 65 | 53 | 5.6 | 11 |
| Urea, 1,3-bis (2-chloroethyl)-1-nitroso | 1.5 | 9.6 | 42 | 3.8 | 3.8 |
| Greishaber and Marsoni, 1986[c] | | | | | |
| Carboplatin | 2.7 | 40 | | | 3.2 |
| Teroxinone | 11 | 27 | | | 8.3 |
| Homoharringtonine | 0.14 | 1.9 | | | 0.15 |
| Fludarabine | 1.1 | 410 | | | 110 |
| Triciribinephosphate | 1.5 | | | | 8.5 |
| *N*-Methylformamide | 32 | 420 | | | 68 |
| DHAC | 68 | 320 | | | 12 |
| Rozencweig et al., 1981[d] | | | | | |
| Anguidine | 0.12 | 9.6 | | | 0.03 |
| Piperazinedione | 0.05 | 1.9 | | | 0.04 |
| Deazuridine | 32 | 190 | | | 64 |
| Gallium nitrate | 3.8 | 10 | | | 1.7 |
| Bakers antifol | 2.7 | 12 | | | 1.0 |
| PALA | 27 | 220 | | | 25 |
| Thalicarpine | 6.0 | 41 | | | 3.3 |
| Maytansine | 0.01 | 0.08 | | | 0.0031 |
| Chlorozotocin | 1.1 | 4.9 | | | 0.15 |
| Paxton et al., 1990[e] | | | | | |
| Amsacrine | 0.62 | 6.92 | | | 0.32 |
| CI-921 | 2.8 | 8.4 | 6.00 | | 0.32 |
| Goldsmith et al., 1975[f] | | | | | |
| 3-(2-Chloroethyl-2-(2-chloroethylamino)) tetrahydro-2H-1, 3, 2-oxazaphosphorine-2-oxide | 27 | | | | 3.2 |
| 3,3′-(Imino) di-1-propanol dimethane sulfonate (ester), hydrochloride | 2.0 | 41 | | 4.7 | 1.3 |
| Cytosine arabinoside[g] | 7.1 | | | 38 | 19 |
| 4-Amino-1-B-d-ribofuranosyl cytosine hydrochloride | 6.8 | 12 | | | 0.52 |
| Tubercidin[h] | 0.50 | | | | 6.4 |
| 2-Amino-9-(2-deoxy-(B-D-erythropentofuranosyl)-9H-purine-6-thiol, hydrate | 8.1 | | | 0.51 | 0.77 |
| 2-Deoxy-2-(3-methyl-3-nitrosoureido) D-glucopyranose | 14 | | | | 3.3 |

**Table 1** (*continued*)

| Source and chemical | Toxic dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | Human | Mouse | Rat | Monkey | Dog |
| Goldsmith et al., 1975[f] | | | | | |
| 4-Amino-7-B-D-ribofuranosyl-7H-pyrrolo(2, 3-d) pyrimidine | 0.95 | 8.7 | | | 0.54 |
| Bleomycin[i] | 0.16 | 12.8 | | 0.11 | 0.27 |
| 3-Acetyl-1, 2, 3, 4, 6, 11-hexahydro-3, 5, 12-trihydroxy-7 (or 10)-methoxy-6,11-dioxo-1-naphthacenyl-3-amino-2, 3, 6-trideoxy-2-a-l-lyxo-hexopyranoside hydrochloride | 1.2 | 1.4 | | 0.73 | 1.2 |
| 5-(3,3 Dimethyl-1-triazeno)-imidazole-4-carboxamide | 6.8 | 100 | | 100 | 15 |
| 4,5-Dicarboxytetrahydro-6-methylene-pyran-2-succinic anhydride, dianhydride, 2,6B polymer | 34 | | | 23 | 12 |
| 2′-(9,10-Anthrylenedimethylene) bis-2-pseudothiourea dihydrochloride dihydrate | 4.1 | 90 | | 16 | 14 |
| 3-Ethyl-1,3,4,6,7,11b-hexahydro-9, 10-dimethoxy-2-[(1,2,3,4-tetrahydro-6, 7-dimethoxy-1-isoquinoly) methyl] -2H-benzo[a] quinolizine, dihydrochloride | 0.30 | 7.4 | | 0.87 | |
| 2-Ethyl-9,11-dihydro-8-(hydroxymethyl)-9-oxo-indolizino [1,2-b] quinoline 7-glycolic acid, sodium salt | 0.54 | 4.0 | | 1.3 | 0.45 |

[a] MTD and other doses, normalized to a 5-day dosing schedule. When necessary, doses were converted to mg/kg from mg/m$^2$ as follows: (dose in mg/kg)=(dose in mg/m$^2$)/*k*; where *k* is a species-specific conversion factor (human)=37; (mouse)=3.0, (rat)=5.2, monkey=11.5, and; dog=19.4.
[b] Human dose=MTD, Mouse=$LI0_{10}$, Rat=$LD_{10}$, Monkey=MTD, Dog=MTD.
[c] Human dose=MTD, Mouse=$LD_{10}$, Dog=$LD_{10}$.
[d] Human dose=MTD, Mouse=$LD_{10}$, Dog=TDL. Dosage converted from a single administration.
[e] Human, rat, and mouse doses=MTD. Dosage converted from a single administration.
[f] Human dose=MTD, Mouse=LD10, Dog=TDL.
[g] Dosage converted from a 10-day schedule.
[h] Dosage converted from a 21-day schedule.
[i] Dosage converted from a bi-weekly schedule.

5. *The majority of the compounds are direct-acting compounds known to have significant biological activity in rapidly dividing cells and may not be fully relevant to the universe of general chemicals.* RfDs are established for a variety of substances including essential nutrients, industrial chemicals, pesticides, metals, inorganics and organics. The substances with existing RfDs, or potentially requiring RfDs, include compounds that are direct acting, compounds that require metabolic activation, compounds with receptor-mediated effects, and compounds that act through more general mechanisms. The impact of this greater heterogeneity may result in greater variance than the MTD ratios.
6. *Human MTD data are drawn from individuals with advanced stages of cancer, and as such may overestimate the toxicity of the compounds for typical humans.* The stress from cancer may reduce the ability of the patients to tolerate the effects of the agents. This would tend to lower the values of the human MTD and raise the value of the ratios. In addition, the condition of the patients could vary from one study to another and may contribute to the variance in the data.
7. *Ratios of MTDs (and other dose metrics) reflect both variation in toxicity between the species and uncertainty in the measurement of the MTD. Thus the distribution of MTD ratios will tend to have greater variance than the true animal to human variability.* The uncertainty in the toxicological measurements used to define the ratios has been discussed by Brand et al. (1999, 2001) and Slob and Peiters

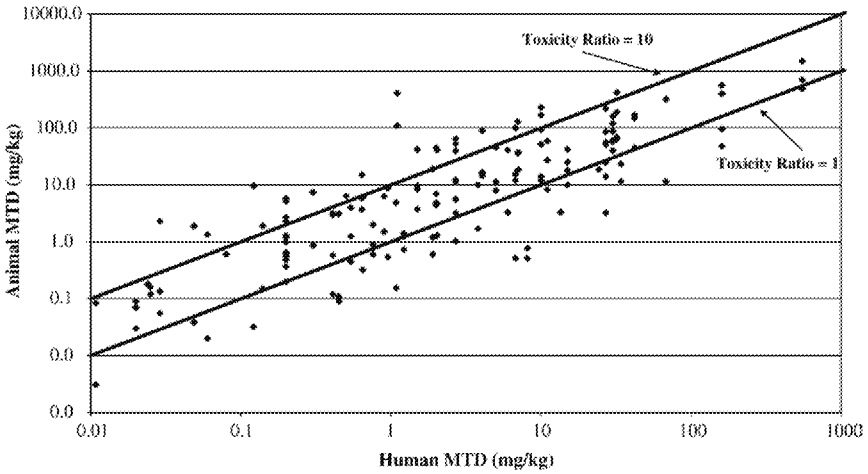


**Fig. 1.** Scatter plot of animal and human MTDs.

(1998). This uncertainty comes from the impact of dose spacing, background rates of adverse effects, and the finite number of animals used in the studies. The effect of this measurement uncertainty is to inflate the variation in the empirical ratios. While the published work has focused on NOAELs and benchmark doses, similar inflation would be expected in the measures of the MTD. In fact, the inflation of the interspecies differences may be more pronounced for the MTD ratios since MTD studies are conducted on smaller numbers of test animals (or humans) than are studies that have generated NOAELs.

Because of these differences, it is not clear that the empirical distributions can be applied directly as measures of uncertainty in the differences between animal and human NOAELs. This issue is addressed in more detail in the discussion section of this paper.

## Analyses of data

Fig. 1 presents a scatter plot of the 161 data points. The plot also includes two lines, one corresponding to equivalent human and animal toxicity and the second to a 10-fold higher sensitivity in humans.

### *Development of species-specific distributions*

Toxicity ratios are likely to differ as a function of the species of the test animal (Travis and White, 1988). For this reason it is important to characterize inter-chemical variation in the ratios as a function of the species of the test animal. This can be done by developing species-specific distributions or by seeking to minimize species differences by using different dose metrics such as body weight$^{3/4}$ or surface area (Travis and White, 1988; Watanabe et al., 1992; Baird et al., 1996; Schneider et al., 2004; Bokkers and Slob, 2007). In this paper, the first approach of developing species-specific distributions is used, as this approach is the one most closely related to application of uncertainty factors in the U.S. EPA RfD methodology (Barnes and Dourson, 1988; USEPA, 2007). The toxicity ratios were sorted by test animal and ranked in order of increasing value. The resulting cumulative distributions are presented in Fig. 2. Summary statistics for the distributions are given in Table 2.

The species-specific distributions were tested to determine if they differed statistically from one another. This was determined using 90% confidence limits on the medians and 90th percentiles of the distributions. The confidence limits were determined using the non-parametric bootstrap approach described below.

### *Evaluation of the impact of data in multiple species*

Where data are available for multiple species the current practice is to use the most sensitive species (on a body weight basis) to establish an RfD (Barnes and Dourson, 1988; USEPA, 1988). Such a practice should have the effect of minimizing the chance of underestimating the toxicity of a compound in humans, as species with greater sensitivity to a compound

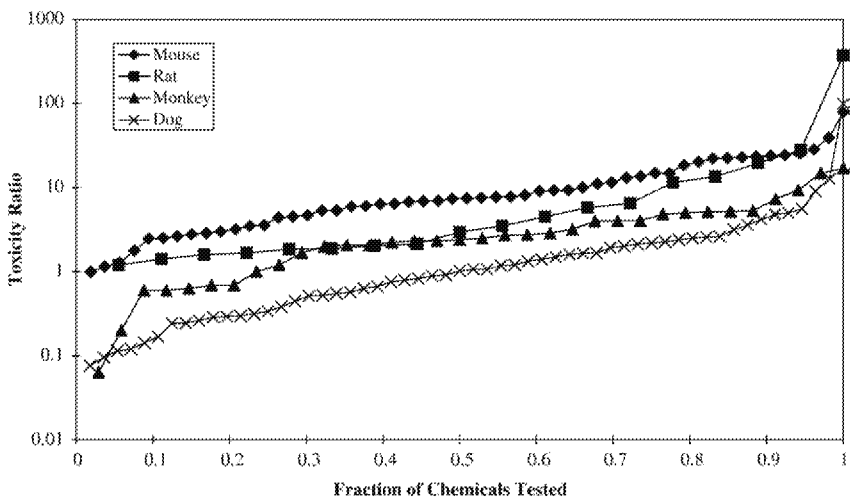


**Fig. 2.** Distribution of toxicity ratios in test animals and humans for four test species.

**Table 2**
Summary statistics for species-specific distributions of toxicity ratios

| | Mouse/human | Rat/human | Monkey/human | Dog/human |
|---|---|---|---|---|
| Number of agents | 54 | 17 | 34 | 56 |
| Median (CI) | 7.7 (6.8–9.3) | 3.0 (1.9–5.8) | 2.5 (2.1–3.3) | 1.0 (0.7–1.5) |
| Mean | 20 | 6.5 | 3.6 | 3.5 |
| 90th percentile (CI) | 25 (23–63) | 16 (6.5–28) | 6.7 (5.0–14) | 4.4 (2.6–7.7) |
| Standard deviation | 51 | 7.6 | 3.7 | 13 |

would be used to establish the RfD. The impact of this practice is examined by plotting the ratio of the lowest test-animal dose to the human MTD in the subset of agents (14 compounds) that have toxicity data for all four species. Fig. 3 presents the distributions of ratios of human MTDs to the lowest MTD for specific combinations of test animals. The combinations consisted of: the mouse dose; the lower of the doses for mouse or rat; the lowest of the doses for mouse, rat, and monkey; and, the lowest of the doses for mouse, rat, monkey, and dog. These combinations were selected based on increasing body weight of the test animals.

*Evaluating the effect of the limited number of compounds on the distribution*

As discussed above, the database for anti-neoplastic agents is relatively small and varies with the test species. An empirical distribution of a relatively small number of chemicals, as in the database for anti-neoplastic agents, is likely to underestimate the true range of the distribution, resulting in potentially significant uncertainty in the estimate of the values of specific percentiles of the distribution. As recommended by Brand et al. (2001), a bootstrap analysis was performed to determine the confidence limits for the means and 90th percentiles (Efron and Tibshirani, 1993). Using unbounded parametric distributions (such as normal or lognormal distributions) has the advantage in that they allow the sampling of plausible values that occur outside of the range of the observed data. Sampling the raw data will limit the values that can be selected and will result in an underestimation of the uncertainty at the extreme tails of the distribution. However, several of the species-specific data sets showed significant deviation from parametric fits (e.g., lognormal). Therefore, the use of unbounded parametric sampling is not appropriate. Sampling in this analysis is performed using an empirical cumulative distribution that allows sampling of values between the raw data points but is still bounded by the range of reported data. Because of this limitation, no estimates were made for the confidence limits of the highest portions of the distributions (>90th percentile).

For this analysis, 10,000 bootstrap samples were generated. In this study, we found that taking 10,000 samples generated stable estimates (within 2%) of the uncertainty in the 90% confidence limits for the medians and the 90th percentiles.

## Results

The data set spans a wide range of toxicity in both test animals and humans (Fig. 1). In general, the toxicity ratios are greater than 1.0 suggesting that the healthy test animals are, on the whole, less sensitive than the human cancer patients when dose is expressed on a body weight basis. In addition, a sizable fraction of the data points (29 of 161) had ratios greater than 10. The size of the ratios varies by species and is larger in species with smaller body weights (Fig. 2). As is displayed in Table 2, the median values for the ratios vary from 1 to 8, or approximately one order of magnitude. The results of the bootstrap analysis provide confidence limits to the estimate of the median and 90th percentile (Table 2). These confidence limits indicate that the medians and 90th percentiles of the distributions of ratios for several of the species overlap and thus some of the species differences in this data set are not statistically significant.

All species had ratios that exceeded 10. The fractions of the compounds with values above 10 were approximately 3%, 5%, 19%, and 37% for the dog, monkey, rat, and mouse. Having data on more than one species tended to reduce the sizes of ratios in the set of compounds with data on all four test species. In the subset of 14 drugs that had data on all four species, use of the lowest MTD from both rats and mice versus the lowest mouse MTD results a reduction of the fraction of compounds with values greater than 10 from 25% to 15%. Data from rats or mice when combined with either the dog or monkey data eliminated values of ratios above 10. The median values of the distributions were reduced by up to a factor of five (Fig. 3).

The results from the bootstrap analysis in Table 2 indicate that there is considerable uncertainty in the estimate of the median and the 90th percentiles of the species-specific distributions. Estimates of the 90% confidence interval of the 90th percentile of each species' ratios show that the number could vary by a factor of 2.7 to 4.3. The uncertainties in the median values are slightly smaller, with the differences in the 90% confidence intervals varying by a factor of 1.4 to 3.1.

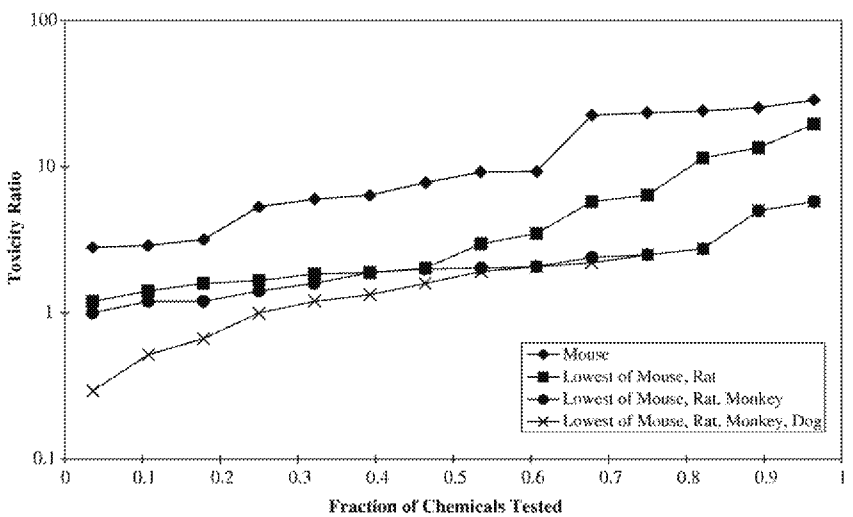


**Fig. 3.** Distribution of toxicity ratios of humans and the most sensitive species in a battery of test species.

## Discussion

The anti-neoplastic data, matched in humans and test animals, provide a unique opportunity to investigate the relationship between the toxicity of this set of chemicals in test animals and human cancer patients. However, as discussed above, there are a number of limitations to the data set.

The issues raised by the limitations can be organized in terms of the impact on likely relationships between the empirical distributions and the uncertainty in the differences between test animals and human toxicity for a chemical. The data set addresses an endpoint that is associated with frank effects rather than NOAELs or LOAELs. Thus, these data are not necessarily representative of the animal to human differences in equivalent-effect doses in the region of interest at the lower end of the dose–response continuum. Similar to $ED_{50}$-based ratios, MTD-based ratios will tend to underestimate the desired ratios (at low dose) to the extent that human response variance exceeds that for test species. On the other hand, to the extent that the human cancer patients in these studies represent a sensitive subpopulation (i.e., older and in poor health), the ratios will tend to be overestimated. Indeed, this limitation of our study has important implications for the selection of an uncertainty factor distribution for interindividual variation as the human subjects were almost certainly compromised. The differences in the severity of the endpoints in the different species may also affect the means of the distributions. None of these potential biases can be quantified at this time.

Three characteristics of the data set will tend to minimize the variation in ratios. These are 1) the use of acute rather than chronic toxicity data, 2) parenteral route of administration (intravenous or intraperitoneal) and 3) the use of agents that in general do not require metabolic activation. Future work should seek to determine the magnitude of additional uncertainty that these factors cause in interspecies extrapolation.

Finally, as discussed by Brand et al. (1999, 2001), measures of ratios of empirical toxicity reflect both the true differences between the test animal and humans, and the experimental uncertainty in the measurements of toxicity. Brand correctly notes that NOAELs and benchmark doses are inherently "messy" measurements, subjected to a number of significant and poorly characterized sources of uncertainty. In addition, limited sample sizes and the large range of values result in wide confidence limits. While Brand did not investigate uncertainty in the MTDs, the same issues that affect NOAELs and benchmark doses affect the MTD. Brand found that this measurement of uncertainty inflated the observed ratios. If this is the case, then the above distributions may overestimate the upper bound (90th percentile) values of the distributions. Additional work in this area is needed.

Despite these limitations in the data, a number of findings are supported by these analyses. First, the ratios of the MTD are generally consistent with traditional assumptions concerning interspecies variation in toxicity for direct-acting compounds. All of the test animals evaluated tend to have toxicity ratios of 1 or more, which supports the use of values greater than 1 for the interspecies uncertainty factor.

Second, ratios generally are larger for smaller animals. Some of this difference may be a reflection of differences in toxicity quantification, that is, impacts in small animals were measured as lethality (LD10s) and large animal toxicity was determined using less-than-lethal endpoints (TDLs). Nonetheless, it appears from this analysis that body weights are an important factor in accounting for interspecies adjustments and that the differences in sensitivity drop coincidentally with converging weights.

Third, the effect of species is not large in comparison to inter-chemical variation. The difference in the median and 90th percentile across species is less than 8-fold. In contrast, the inter-chemical variations in the toxicity ratios of each species' range of data exceed two orders of magnitude. Fourth, up to 37% of the agents tested in a given species had ratio values greater than 10. This finding may be influenced by the contribution of measurement uncertainty in the MTDs. Fifth, where data are available in multiple species, the probability of large values for a ratio is decreased. For example, the 90th percentile of the distribution for the mouse is 5 times higher than the 90th percentile of the distribution of ratios for the lowest endpoint of the mouse, rat, dog, and monkey. This suggests that a lower interspecies extrapolation factor is appropriate for compounds with relevant toxicity data in multiple species than would be indicated by the species-specific MTD ratio distribution alone. Finally, the bootstrapping analysis shows the impact of limited sample size on the uncertainty in the estimates of the median and 90th percentile of the distribution. The difference between the 90% confidence limits ranges up to a factor of 4.3. Increasing the number of agents would provide a significant improvement in the characterization of interspecies variation.

## Conclusion

The distributions developed in this paper are a relevant source of information on the uncertainty in the differences in test animal models and humans and provide a starting point for future research in the relationship between animal and human toxicity for probabilistic noncancer models. Although limited by a number of factors, the empirical data set on toxicity ratios in anti-neoplastic agents is one of the largest in the published literature for the characterization of interspecies uncertainty. The work in this paper establishes the importance of considering the total number of species tested when evaluating the uncertainty in extrapolating findings from animal models to humans. Finally, this work demonstrates the value of additional efforts to collect and evaluate data on anti-neoplastic agents for improving probabilistic non-cancer risk assessments.

## Conflict of interest disclosure statement

The authors declare that they have no conflicts of interest.

## Acknowledgments

This paper was initially developed as part of the cooperative research and development agreement (CRADA) between McLaren/Hart Environmental Engineering Corporation and the U.S. Environmental Protection Agency under the U.S. Federal Technology Transfer Act of 1996. The paper was revised with additional support from General Electric and The Dow Chemical Company. The views expressed in this paper are of the authors and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency.

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Message

**From**: Goldstein, Bernard D [bdgold@pitt.edu]
**Sent**: 11/16/2017 8:57:02 PM
**To**: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; White, Kimberly [Kimberly_White@americanchemistry.com]; rdenison@edf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b2358277ea84ca2a4375a8b8744a7af-rdenison@edf.org]; Terry F. Yosie [tyosie@wec.org]; Joe Arvai [jlarvai@umich.edu]
**Subject**: FW: SRA 2017 Annual Meeting Roundtable Acceptance

Hi everyone

Below is a note from Terje Aven of SRA about our Roundtable. We seem to have picked a timely topic.

At the bottom I've appended my original note following acceptance and a copy of the abstract. The plan is for:

1:30pm Terry to give a very short introduction, including making it clear that the focus is on the "underlying principles" as per the last sentence of the abstract;
1:35pm each of us will speak for **no more than 10 minutes,** and I hope less
2:25pm Terry will then ask some questions to get the discussion going, again focusing on "underlying principles";
2:40pm Terry will then ask for questions from the floor.

I hope our responses to all questions can be brief. As the above schedule only gives 20 minutes to questions from the floor, it would be helpful if we can each cut a few minutes from our presentation

To be decided yet is order of speakers. Best spot, of course, is last as it gives the speaker a chance to rebut earlier speakers. Let me suggest the following: Goldstein, Beck, Arvai, Denison, White. Am open to other suggestions, with a coin toss as ultimate decision maker.

Note instructions below from Jennifer Rosenberg include the request that all powerpoints be uploaded by December 4th - and we need to be registered. Terje also asks that we have a planning meeting by phone beforehand. In view of how much time we spent earlier on the framework of this Roundtable, am not sure this is needed -- and I shudder at the thought of finding a time we can all get on a phone line in the next few weeks. So unless someone wants to hold such a pre-meeting, I suggest we skip it. Would of course be happy to talk to any of you individually

Best regards

Bernie

Bernard D. Goldstein, MD
Professor Emeritus and Dean Emeritus
University of Pittsburgh Graduate School of Public Health
Rm A710, Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
412 648 9994

**From:** Terje Aven [mailto:terje.aven@uis.no]
**Sent:** Thursday, November 16, 2017 10:43 AM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Subject:** VS: SRA 2017 Annual Meeting Roundtable Acceptance

Hi Bernard,

Thanks a lot for organizing and chairing this Roundtable (RT).
It looks very interesting.
I understand that Jennifer has been in contact with you concerning the RT chairs and panelists. The program is soon to be printed, so hope everything is fine on that point.

RTs can be structured and run in different ways, but in line with good SRA practice they should include well-prepared introduction talks by all panelists (3-10 m depending on the number of panelists and other features of the RT), and the Chair/Moderator of the RT should have had a process with the panelists in advance of the meeting to highlight the key issues/questions to be discussed.

Please contact me if you have any questions related to this
(I write such emails to all RT chairs, I know this one will be great).

I look very much forward to the RT.

Best
Terje Aven
Chair of SRA 2017 Program Committee

---

Jennifer Rosenberg, CMP
Director, Meetings and Events
1313 Dolley Madison Blvd.
Suite 402
McLean VA 22101
703-790-1745 Ex. 6
Fax: 703-790-2672
jrosenberg@burkinc.com

Begin forwarded message:

**From:** jennifer Rosenberg <jrosenberg@burkinc.com>
**Subject: SRA 2017 Annual Meeting Roundtable Acceptance**
**To:** bdgold@pitt.edu

# Subject: SRA 2017 Annual Meeting Roundtable Acceptance

What is the Optimal Approach to Organizing Governmental Risk-Related Science Advisory Processes

has been accepted for the 2017 Meeting in Arlington, VA on

10-14 December as a

on Tuesday, December 12, from 1:30 PM to 3:00 PM. The online program will be available by August 15. You will be able to view it by going to http://sra.org/events/sra-2017-annual-meeting

Please note that all persons attending the Annual Meeting (or any part thereof) are **REQUIRED** to pay the appropriate registration fee as indicated on the registration form. Most importantly, **ALL PRESENTERS IN YOUR ROUNTABLE SESSION MUST REGISTER FOR THE MEETING.** (Registration will open at the end of August at www.SRA.org.) If for any reason you need to cancel your presentation, as a courtesy to the Society and the other meeting participants, please contact your session chair, the Annual Meeting Committee chair (Terje Aven, terje.aven@uis.no), AND Jennifer Rosenberg of the SRA Secretariat (jrosenberg@burkinc.com) as soon as possible.

Please upload all Powerpoint presentations for your session by December 4 at http://burkinc.net/sraAM/index.php3. Instructions for the upload of your presentation will be posted at www.sra.org after 30 September. It is very important that you follow these instructions and upload before the meeting so the session will run smoothly.

Please go to www.sra.org to view the preliminary program and information for registering for the meeting (which will be posted soon). A room block has been set aside at the Crystal Gateway Marriott. Reservations can be made at the special SRA rate by using this link - https://aws.passkey.com/event/49022912/owner/1487/home

Thank you for your participation. We look forward to seeing you in Arlington in December.

Terje Aven

SRA President-Elect and Annual Meeting Chair

Jennifer Rosenberg

Director, Meetings and Events

Jennifer Rosenberg, CMP
Director, Meetings and Events
1313 Dolley Madison Blvd.
Suite 402

McLean VA 22101
703-790-1745 Ex. 6
Fax: 703-790-2672
jrosenberg@burkinc.com

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Congratulations to us all. We are on the schedule for Tuesday afternoon, 12/12, from 1:30-3pm.

Just as a reminder:. The final order of presentations is open – it will be ten minutes each except for Terry who is our MC. Should leave 40 min for discussion. Again, the focus should be on the optimal principles and how best to achieve them rather than a critique of specific legislation. Our abstract is below

*Recent activities by both Congress and by EPA Administrator Pruitt provide an opportunity to evaluate approaches for organizing risk-related scientific advisory processes for regulatory agencies. The EPA Science Advisory Board Reform Act has been passed by the US House of Representatives and is awaiting action in the US Senate, which may or may or may not be forthcoming. These have generated media interest and controversy and some have characterized these actions as unnecessarily politicizing science and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes. Others have pointed out that there is a need to broaden scientific representation in diverse fields, and to improve procedures for balancing perspectives and perceived biases on EPA scientific advisory panels. The Roundtable participants will be asked to focus on the underlying principles that should guide the science advisory processes for the optimal provision of scientific advice on risk-related issues to a regulatory agency.*

Hope you are all having a good summer

Bernie

## Subject: SRA 2017 Annual Meeting Roundtable Acceptance

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Please note that all persons attending the Annual Meeting (or any part thereof) are **REQUIRED** to pay the appropriate registration fee as indicated on the registration form. Most importantly, **ALL PRESENTERS IN**

**YOUR ROUNTABLE SESSION MUST REGISTER FOR THE MEETING.** (Registration will open at the end of August at www.SRA.org.) If for any reason you need to cancel your presentation, as a courtesy to the Society and the other meeting participants, please contact your session chair, the Annual Meeting Committee chair (Terje Aven, terje.aven@uis.no), AND Jennifer Rosenberg of the SRA Secretariat (jrosenberg@burkinc.com) as soon as possible.

Please upload all Powerpoint presentations for your session by December 4 at http://burkinc.net/sraAM/index.php3. Instructions for the upload of your presentation will be posted at www.sra.org after 30 September. It is very important that you follow these instructions and upload before the meeting so the session will run smoothly.

Please go to www.sra.org to view the preliminary program and information for registering for the meeting (which will be posted soon). A room block has been set aside at the Crystal Gateway Marriott. Reservations can be made at the special SRA rate by using this link - https://aws.passkey.com/event/49022912/owner/1487/home

Thank you for your participation. We look forward to seeing you in Arlington in December.

Terje Aven

SRA President-Elect and Annual Meeting Chair

Jennifer Rosenberg

Director, Meetings and Events

Jennifer Rosenberg, CMP
Director, Meetings and Events
1313 Dolley Madison Blvd.
Suite 402
McLean VA 22101
703-790-1745 Ex. 6
Fax: 703-790-2672
jrosenberg@burkinc.com

Message

**From:** Jennifer Tanir[Ex. 6]
**Sent:** 10/16/2017 2:10:18 PM
**To:** Richard E. Engler, Ph.D. [rengler@lawbc.com]
**CC:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com;[Ex. 6]; Ashley Black [ashley@toxicology.org]
**Subject:** Re: Thanks to each of you--Oct 13 NCAC/CSW symposium

I echo Meg's sentiments - thank you all for your time and active participation! I learned a lot from the excellent presentations and discussions. And that most of the participants in the room and on the webinar stayed until the end was a testament to their interest!

Best,
Jen

Jennifer Y. Tanir, PhD
Founder and Consultant
Toward Safer LLC
jentanir@towardsafer.com
www.towardsafer.com

On Sun, Oct 15, 2017 at 8:27 PM, Richard E. Engler, Ph.D. <rengler@lawbc.com> wrote:

> Thank you for giving us an opportunity to discuss some of these critical issues and places where we agree and disagree!
>
> Rich
>
> **RICHARD E. ENGLER, PH.D.**
>
> **SENIOR CHEMIST**
>
> BERGESON & CAMPBELL PC
>
> 2200 Pennsylvania Avenue, N.W. Suite 100W | Washington, D.C. 20037
>
> T: 202-557-3808 | F: 202-557-3836 | lawbc.com

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, October 13, 2017 7:01 PM
**To:** mwhittaker@toxservices.com
**Cc:** Jennifer Tanir; Richard E. Engler, Ph.D.; jsass@nrdc.org; Devito, Steve; Henry, Tala; Kimberly_White@americanchemistry.com; Ex. 6 Ashley Black
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Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

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<image001.gif>

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**Ex. 6**

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**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]
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Message

**From:** Henry, Tala [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=8BFC0A617A4A43BAA8856541C70622BE-THENRY02]
**Sent:** 10/14/2017 3:53:11 PM
**To:** Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]
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**Subject:** RE: Thanks to each of you--Oct 13 NCAC/CSW symposium

A day later...but still, I concur with all others, it was an excellent program and the panel Q&A and discussion was very helpful, I think, in message out for us and hopefully providing more clarity about how things fit together for the attendees.

Thanks again for the invite!

Tala R. Henry, Ph.D.
Director, Risk Assessment Division
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency

T: 202-564-2959
E: henry.tala@epa.gov

**From:** Devito, Steve
**Sent:** Friday, October 13, 2017 7:36 PM
**To:** mwhittaker@toxservices.com
**Cc:** Jennifer Tanir Ex. 6 ; Beck, Nancy <Beck.Nancy@epa.gov>; Richard E. Engler, Ph.D. <rengler@lawbc.com>; jsass@nrdc.org; Henry, Tala <Henry.Tala@epa.gov>; Kimberly_White@americanchemistry.com; Ex. 6 Ashley Black <ashley@toxicology.org>
**Subject:** Re: Thanks to each of you--Oct 13 NCAC/CSW symposium

Meg:

Thank you. My compliments to you on organizing such well-rounded meeting. It was a pleasure to be a part of it.

Sincerely,
Steve DeVito

Sent from my iPhone

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Message

**From:** White, Kimberly [Kimberly_White@americanchemistry.com]
**Sent:** 10/13/2017 11:08:04 PM
**To:** mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]; Jennifer Tanir Ex. 6 Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Richard E. Engler, Ph.D. [rengler@lawbc.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Ex. 6
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Thank you Meg, ACS and NCAC for putting together the session and inviting me to join. It was a good discussion.

-------- Original Message --------
Subject: Thanks to each of you--Oct 13 NCAC/CSW symposium
From: Margaret Whittaker <Mwhittaker@toxservices.com>
Date: Oct 13, 2017, 6:21 PM
To: Jennifer Tanir Ex. 6 ,beck.nancy@epa.gov,"Richard E. Engler, Ph.D." <rengler@lawbc.com>,jsass@nrdc.org,Steve Devito <Devito.Steve@epa.gov>,Henry.Tala@epa.gov,"White, Kimberly" <Kimberly_White@americanchemistry.com> Ex. 6
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**From**: Kenneth A Mundt [kmundt@ramboll.com]
**Sent**: 10/3/2017 9:49:42 PM
**To**: Camacho, Iris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5598d2cc8e3c4302aff255a840a991dc-Camacho, Iris]
**CC**: jswenber@email.unc.edu; White, Kimberly [Kimberly_White@americanchemistry.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject**: RE: Invitation to Formaldehyde Expert Workshop at UNC

Dear Iris,

Wonderful! We welcome your participation. Indeed there is no registration fee.

I have cc'd Dr. Kimberly White of the ACC, and she will send you the participant's information package, including the agenda.

Please do not hesitate to contact Kimberly or me with any questions, and we very much look forward to seeing you in NC next week.

Yours sincerely
**Kenneth A. Mundt, PhD, FACE**

Health Sciences Practice Network Leader

D
M **Ex. 6**
kmundt@ramboll.com

Ramboll Environ
28 Amity Street
Suite 2A
Amherst, MA 01002
USA
www.ramboll-environ.com


**From:** Camacho, Iris [mailto:Camacho.Iris@epa.gov]
**Sent:** Tuesday, October 03, 2017 4:40 PM
**To:** Kenneth A Mundt
**Cc:** jswenber@email.unc.edu
**Subject:** RE: Invitation to Formaldehyde Expert Workshop at UNC

Hi Ken,
I will be attending the formaldehyde workshop. Itis my understanding that you were notified that I will be the person representing EPA/OPPT (TSCA program).

I assume that no registration fees are required. I did not claim them in my travel authorization. I will appreciate a copy of the agenda.

Thanks.

**********

Iris A. Camacho, Ph.D.
Senior Science Advisor (on detail)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
William Jefferson Clinton Building East, 6308-A
Washington, DC 20460
Phone: 202-564-1229
Work hours: Ex. 6
Work cell phone: Ex. 6
Telework phone: Ex. 6
Email: camacho.iris@epa.gov

---

**From:** Kenneth A Mundt [mailto:kmundt@ramboll.com]
**Sent:** Wednesday, September 20, 2017 10:48 AM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Cc:** Swenberg, James A <jswenber@email.unc.edu>
**Subject:** Invitation to Formaldehyde Expert Workshop at UNC

Dear Dr. Beck,

Dr. Jim Swenberg and I are co-hosting an Invited Expert Workshop on the latest formaldehyde science and approaches to evidence integration, with an objective of identify the best path(s) forward for formaldehyde risk assessment. We are pleased to extend an invitation to you (please see attached invitation letter), and would be honored if you could join.

Please do not hesitate to contact me with any questions you may have. A full agenda for the meeting is close to being finalized, and I would be happy to share that with you as soon as it is.

Thank you for your consideration, and we hope to see you Chapel Hill.

Best,

Ken

Yours sincerely
**Kenneth A. Mundt, PhD, FACE**

Health Sciences Practice Network Leader

RAMBOLL ENVIRON www.ramboll-environ.com

Secretary General

MEDICHEM www.medichem.org

D Ex. 6
M
kmundt@ramboll.com

Ramboll Environ
28 Amity Street
Suite 2A
Amherst, MA 01002
USA

Message

**From**: Bridgeford, Tawny [TBridgeford@nma.org]
**Sent**: 9/22/2017 1:40:18 PM
**To**: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject**: Automatic reply: Invitation to Speak at NMA's Environment Committee Meeting in October

I am currently out of the office and will return on Tuesday, Sept. 26. If you need immediate assistance please contact Paige Rotunda at protunda@nma.org.

Message

**From**: Margaret Whittaker [Mwhittaker@toxservices.com]
**Sent**: 10/6/2017 2:23:18 PM
**To**: Richard E. Engler, Ph.D. [rengler@lawbc.com]; 'Jennifer Tanir Ex. 6 Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com
**CC**: Ashley Black [ashley@toxicology.org]
**Subject**: RE: Important details about Oct 13 NCAC/CSW symposium

Yes! You go first ☺

Meg

Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC
1367 Connecticut Avenue, N.W., Suite 300
Washington, D.C. 20036
(202) 429-8787 (US telephone)
+44(0) 20 3318 3429 (UK telephone)
(202) 429-8788 (fax)
www.toxservices.com

Find us on Facebook!

**From:** Richard E. Engler, Ph.D. [mailto:rengler@lawbc.com]
**Sent:** Friday, October 06, 2017 10:22 AM
**To:** 'Jennifer Tanir' Ex. 6 ; beck.nancy@epa.gov; jsass@nrdc.org; Devito.Steve@epa.gov; Henry.Tala@epa.gov; Kimberly_White@americanchemistry.com
**Cc:** Margaret Whittaker <Mwhittaker@toxservices.com>; Ashley Black <ashley@toxicology.org>
**Subject:** RE: Important details about Oct 13 NCAC/CSW symposium

Can we get the embarrassing stories during the break?

**RICHARD E. ENGLER, PH.D.**
**SENIOR CHEMIST**
BERGESON & CAMPBELL PC
2200 Pennsylvania Avenue, N.W. Suite 100W | Washington, D.C. 20037

T: 202-557-3808 | F: 202-557-3836 | lawbc.com

**From:** Jennifer Tanir Ex. 6
**Sent:** Friday, October 06, 2017 9:37 AM
**To:** beck.nancy@epa.gov; Richard E. Engler, Ph.D.; jsass@nrdc.org; Devito.Steve@epa.gov; Henry.Tala@epa.gov; Kimberly_White@americanchemistry.com
**Cc:** Margaret Whittaker; Ashley Black
**Subject:** Re: Important details about Oct 13 NCAC/CSW symposium

I knew I would forget something! I meant to also ask you to send a **short bio** with your slides, so we can properly introduce you. Meg and I know who you are, but a few sentences will help us get the details right, and can avoid Meg telling some embarrassing story about you :)

Thanks!
Jen

On Fri, Oct 6, 2017 at 8:18 AM, Jennifer Tanir Ex. 6 wrote:
Dear presenters,
Our symposium is just a week away! Thank you so much for agreeing to participate. I have a few deadlines and details to let you know about:

**Presentations:** please provide your presentation to me by **Wednesday, October 11**. The reason is that we are running a webinar of the symposium from SOT headquarters during the live event at ACS headquarters, so we need to copies in both places and make sure they're working. If you have trouble meeting this deadline, please let me know.

**Permission:** please **fill in and return** the attached SOT permission form regarding release of your materials. The webinar will be recorded and posted on the SOT website, along with the slides, pending your permission. If you have questions, please contact Ashley Black at SOT (cc'ed).

**Agenda:** the final symposium agenda is located here: https://www.toxicology.org/groups/rc/ncac/docs/NCAC_CSW_Fall_2017_Symposium_Final_Agenda.pdf
.

**Registration:** you've all been registered for the meeting and received a confirmation email yesterday. Lunch and breaks are included (but no breakfast).

**Numbers/Set-up:** as of yesterday, we have 50+ people registered to attend in person and 40+ registered for the online webinar. The limit in the room will be about 75 people (set 6-8 people around tables). The room is a long rectangle, with stage, podium, microphone, and large screen for your presentation, and additional TV screens towards the back of the room for viewing of the slides. In a side room, we'll have 24 posters by students & postdocs during the poster competition. We'll take questions from the "chat window" of the webinar too, during the Q&A periods.

Please let me or Meg know if you have any questions as you prepare for the symposium!

Best,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary
Ex. 6

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Message

**From:** Richard E. Engler, Ph.D. [rengler@lawbc.com]
**Sent:** 10/6/2017 2:22:00 PM
**To:** 'Jennifer Tanir' [Ex. 6] Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com
**CC:** mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]; Ashley Black [ashley@toxicology.org]
**Subject:** RE: Important details about Oct 13 NCAC/CSW symposium

Can we get the embarrassing stories during the break?

**RICHARD E. ENGLER, PH.D.**
**SENIOR CHEMIST**
BERGESON & CAMPBELL PC
2200 Pennsylvania Avenue, N.W. Suite 100W | Washington, D.C. 20037
T: 202-557-3808 | F: 202-557-3836 | lawbc.com

**From:** Jennifer Tanir [Ex. 6]
**Sent:** Friday, October 06, 2017 9:37 AM
**To:** beck.nancy@epa.gov; Richard E. Engler, Ph.D.; jsass@nrdc.org; Devito.Steve@epa.gov; Henry.Tala@epa.gov; Kimberly_White@americanchemistry.com
**Cc:** Margaret Whittaker; Ashley Black
**Subject:** Re: Important details about Oct 13 NCAC/CSW symposium

I knew I would forget something! I meant to also ask you to send a **short bio** with your slides, so we can properly introduce you. Meg and I know who you are, but a few sentences will help us get the details right, and can avoid Meg telling some embarrassing story about you :)

Thanks!
Jen

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Please let me or Meg know if you have any questions as you prepare for the symposium!

Best,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary

**Ex. 6**

Message

**From:** Jennifer Tanir [Ex. 6]
**Sent:** 10/12/2017 4:02:31 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Richard E. Engler, Ph.D. [rengler@lawbc.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com; [Ex. 6]
**CC:** mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]; Ashley Black [ashley@toxicology.org]
**Subject:** Re: Important details about Oct 13 NCAC/CSW symposium
**Attachments:** Permissions Release for SOT Use of Materials.pdf; Tracking presenter files.xlsx

Dear Presenters,
Please send me your presentations, short bios, and SOT permission form (attached) by this afternoon. The attached table summarizes the materials I've received so far.

Tomorrow's program starts early, so we would like to have everything in place by later today. Also, SOT will be running and recording a live webinar during the symposium, so we need to make sure we have the permissions in place in advance.

If you have any questions, please don't hesitate to contact me anytime! My cell is [Ex. 6]. It should be an excellent symposium!

Thanks,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary

On Fri, Oct 6, 2017 at 9:36 AM, Jennifer Tanir [Ex. 6] wrote:

> I knew I would forget something! I meant to also ask you to send a **short bio** with your slides, so we can properly introduce you. Meg and I know who you are, but a few sentences will help us get the details right, and can avoid Meg telling some embarrassing story about you :)
>
> Thanks!
> Jen
>
> On Fri, Oct 6, 2017 at 8:18 AM, Jennifer Tanir [Ex. 6] wrote:
>
> > Dear presenters,
> > Our symposium is just a week away! Thank you so much for agreeing to participate. I have a few deadlines and details to let you know about:
> >
> > **Presentations:** please provide your presentation to me by **Wednesday, October 11**. The reason is that we are running a webinar of the symposium from SOT headquarters during the live event at ACS headquarters, so we need to copies in both places and make sure they're working. If you have trouble meeting this deadline, please let me know.

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Please let me or Meg know if you have any questions as you prepare for the symposium!

Best,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary
**Ex. 6**

SOT | Society of Toxicology

1821 Michael Faraday Drive, Suite 300
Reston, Virginia 20190
Tel: (703) 438-3115 Fax: (703) 438-3113
E-mail: sothq@toxicology.org
Web site: www.toxicology.org

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| Author: Printed Name | Signature | Date |
|---|---|---|

Return completed and signed form to SOT Attention: Tierre Miller
1821 Michael Faraday Drive Suite 300
Reston, Virginia 20190
FAX: 703 438-3113 or PDF to tierre@toxicology.org

Rev. 7/22/11

| Presenter | Bio | Slides | Permission form |
|---|---|---|---|
| Nancy Beck | | Yes | |
| Richard Engler | | | |
| Jennifer Sass & Bob Sussman | Yes | | |
| Stephen DeVito | | | (Yes) |
| Tala Henry | | | |
| Kimberly White | Yes | Yes | |

Message

**From:** Jennifer Tanir [Ex. 6]
**Sent:** 10/6/2017 1:36:37 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Richard E. Engler, Ph.D. [rengler@lawbc.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com
**CC:** mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]; Ashley Black [ashley@toxicology.org]
**Subject:** Re: Important details about Oct 13 NCAC/CSW symposium

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Thanks!
Jen

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>
> **Presentations:** please provide your presentation to me by **Wednesday, October 11**. The reason is that we are running a webinar of the symposium from SOT headquarters during the live event at ACS headquarters, so we need to copies in both places and make sure they're working. If you have trouble meeting this deadline, please let me know.
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Please let me or Meg know if you have any questions as you prepare for the symposium!

Best,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary
Ex. 6

Message

**From:** Bridgeford, Tawny [TBridgeford@nma.org]
**Sent:** 9/19/2017 6:09:32 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** Invitation to Speak at NMA's Environment Committee Meeting in October
**Attachments:** Ms. Beck Invite.pdf

Nancy:

On behalf of the National Mining Association, I am writing to invite you to speak at our Environment Committee meeting on Oct. 16 or 17, 2017, in Washington, D.C. Details regarding the meeting are in the attached formal invitation. We look forward to hearing from you or your staff!

Regards,

Tawny

Tawny Bridgeford
Deputy General Counsel & Vice President, Regulatory Affairs
National Mining Association
101 Constitution Ave. NW, Suite 500 East
Washington, D.C. 20001
Phone: (202) 463-2600
Direct: Ex. 6
tbridgeford@nma.org

Tawny Bridgeford
*Deputy General Counsel & Vice President, Regulatory Affairs*

September 19, 2017

***Via E-mail***

Nancy Beck
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Mail Code 7101M
Washington, DC 20460

Dear Ms. Beck:

On behalf of the National Mining Association (NMA), I would like to invite you to address a broad section of the mining industry at our upcoming meeting of NMA's Environment Committee. NMA represents the producers of most of the nation's coal, metals, industrial and agricultural minerals; the manufacturers of mining and mineral processing machinery, equipment and supplies; and other firms serving the mining industry. NMA's Environment Committee consists of those environmental professionals whose job it is to understand and guide compliance with the many federal, state and local environmental regulations governing mining activities. The meeting is an informal setting that gives our industry representatives a chance to meet with key agency staff that work on their priority issues.

Notably, NMA has a subcommittee of member companies devoted to solid waste and chemical substance issues, including those that arise under the Toxic Substances Control Act and the Emergency Planning and Right-to-Know Act (most notably the Toxics Release Inventory (TRI)). Most recently, NMA has begun educating our members on the recent TSCA reform implementation rules, including the inventory notification requirements and the prioritization and risk evaluation processes. We believe our members would benefit greatly from hearing from you or the appropriate staff on the agency's implementation of these rules and what industry should know from a compliance standpoint. We would also welcome any relevant updates on potential changes or developments in the TRI program.

The meeting will be held on Oct. 16 and 17, 2017, at the Renaissance Washington, D.C. Downtown Hotel located at 999 Ninth Street, N.W., Washington, DC. We would welcome an opportunity for you to meet with our members for 60 minutes during either day. We currently have open speaker slots as follows:

**Monday, Oct. 16**:

1:30 p.m. – 2:30 p.m.

3:45 p.m. – 4:45 p.m.

**Tuesday, Oct. 17**:

8:00 a.m. – 9:00 a.m.

10:45 a.m. – 11:45 a.m.

We welcome hearing from you or your staff. Thank you for your prompt consideration of this outreach opportunity.

Regards,

Tawny A. Bridgeford

Message

**From:** Roy Bailey [rbailey@gdcillc.com]
**Sent:** 7/28/2017 9:36:09 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]
**Subject:** RE: For your assistance

Thanks so much Nancy – sure appreciate everyone's attention to our concern.

Hope you have a great weekend

**Roy W. Bailey**
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, July 28, 2017 4:33 PM
**To:** Roy Bailey <rbailey@gdcillc.com>; Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>
**Subject:** RE: For your assistance

Thanks Roy.
I will pass these along to our experts for their review and input. I will get back to you once I have a sense from them regarding how long a review will take.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Roy Bailey [mailto:rbailey@gdcillc.com]
**Sent:** Friday, July 28, 2017 5:17 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>

**Cc:** Roy Bailey <rbailey@gdcillc.com>
**Subject:** For your assistance

Nancy,

Please find the attachment for you and the team's review. It is a thoughtful and substantive summary of answers and feedbacks to that which was sent to me earlier this week.

I hope you all find this helpful. We are more than happy to get together next week or whenever you think appropriate.

All my respect and regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

> **From:** "Chris Basta (INTREXON CORP)" <cbasta7@bloomberg.net>
> **Date:** July 28, 2017 at 3:49:10 PM CDT
> **To:** undisclosed-recipients:;
> **Subject: Follow-up**
> **Reply-To:** Chris Basta <cbasta7@bloomberg.net>
>
> Roy,
>
> With respect to the email you had sent on Tuesday regarding the scientific publications highlighting concerns or risks surrounding Wolbachia, please see the attached document with feedback to the points that were raised.
>
> Hope you have a great weekend.
>
> Best regards,
> Chris

Message

**From:** Roy Bailey [rbailey@gdcillc.com]
**Sent:** 7/28/2017 9:17:17 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC:** Roy Bailey [rbailey@gdcillc.com]
**Subject:** For your assistance
**Attachments:** Feedback to Points Raised Regarding Publications - 7.28.2017.docx; ATT00001.htm

Nancy,

Please find the attachment for you and the team's review. It is a thoughtful and substantive summary of answers and feedbacks to that which was sent to me earlier this week.

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Overall it appears that an adequate biosafety risk examination of this particular strain of *Wolbachia* (wAlb) in this particular mosquito (*Aedes aegypti*) has not been performed by the applicants. As '*Wolbachia causes very different responses depending on the host*' then each time *Wolbachia* is inserted into a new host it should be fully assessed. The information in publications from numerous independent scientists that cite various risks regarding the use of *Wolbachia* as a vector (i.e., mosquito) control method should be cause for concern.

Below is specific feedback to comments in the email received, as well as the EPA response to public comments from August 2016 that were cited in response to third-party scientist publications that express concerns or note potential issues with *Wolbachia*, including several specifically citing risks for its use in vector control.

1. **Feedback to comments in email received:**

   **Email comment –** *"Citation 5: This research is for a completely different organism, Spodoptera exempta (African armyworm), not mosquitoes, and Wolbachia causes very different responses depending on the host. This information, while interesting, cannot be used to make predictions about mosquitoes."*

   **Feedback** – These two publications listed here are: (1) specific to mosquitoes and (2) involve the wAlbB strain of *Wolbachia*. These are not being cited to make predictions, however they involve mosquitoes as well as the wAlbB strain, and are relevant to a proper risk assessment:

   - *Wolbachia* Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
   - *Wolbachia* Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965

   As noted in EPA comments '*Wolbachia causes very different responses depending on the host*', therefore, every insertion of *Wolbachia* into a new host – like *Aedes aegypti* - should be tested and fully assessed given the interactions are unknown and unpredictable.

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**Email comment** - *Citation 12: With respect to the Wolbachia phage encoding a toxin from the black widow spider, this comment is referring to Citation 12 ("Eukaryotic association module in phage WO genomes from Wolbachia"). In this study, the WO-B phage in wAlbB strain mosquitoes were not studied. Only moth and parasitoid wasp WO phage were researched. Aedes aegypti wAlbB strain does have a WO-B phage associated with it; however, phage are specific to their hosts, horizontal gene transfer is happening on evolutionary time scales, there is no indication that the widow spider toxin sequence is expressed in the Wolbachia infection, and it is not reported that the WO-B phage in wAlbB Aedes aegypti produce the toxin from black widow spider. Also, most importantly, viruses*

*have been shown to incorporate host sequences numerous times, but this is the first report of a virus of an obligate intercellular parasitic bacterium having sequences from both hosts: bacterial and eukaryotic. The widow spider toxin is a huge multimeric toxin with the entire 150kD monomer needing to be expressed and binding to form a tetramer to have full toxin activity. The sequence detected in the prophage sequence is only the C-terminus (maybe 18 kD) of the entire monomeric protein (150 kD). This C-terminus has been implicated in passage through membranes to release the toxins when produced in the spider. Furthermore, there is no evidence that Wolbachia alone are being transferred to animals when a female mosquito bites and takes a blood meal from an animal.*

**Feedback -** Granting an experimental use permit notwithstanding the current lack of understanding of potential adverse effects that may result from the transfer of potentially harmful genes would seem to be inconsistent with EPA's regulatory obligations under FIFRA. It is well known that phage have ability to insert its genes into bacterial genomes. The WO phage (once inserted it's called a prophage) can and does insert into the *Wolbachia* genome – this has been established as per this 2016 publication:

- Eukaryotic association module in phage WO genomes from Wolbachia http://www.nature.com/articles/ncomms13155

This results in genetic transformation that is unknown and uncharacterized, i.e., an unknown transgenic genome. The argument that the spider toxin will not be expressed because it is not the full genome is not the point. What is the C-terminus encoding for? Why is it there? What is the impact of it being there? It is imperative that these questions be addressed and investigated prior to *Wolbachia* being released into the environment in human biting mosquitoes.

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**Email comment –** *Citation 13, 14, and 15: The Wolbachia pipientis strains associated with River blindness and lymphatic filariasis are in different clades than the wAlbB, and the wAlbB strain is not associated with these diseases.*

**Feedback –** The proponents of *Wolbachia* as a potential vector control method continuously cite that ~60% of insects may be infected with *Wolbachia* and therefore it is safe.

This estimate, which is at the highest end of the range of 20% to 60% listed in various publications, covers all *Wolbachia* strains including the clades of *Wolbachia* that are associated with river blindness that has infected over 30 million people in a single year and with lymphatic filariasis that infects an estimated 120 million people in tropical and subtropical areas according to the World Health Organization.

The mechanisms of action of any of the clades of *Wolbachia* are not completely understood and given these statistics and publications, extreme caution should be taken with the artificial introduction into a human biting mosquito.

These publications discuss Wolbachia's association with these devastating diseases that impact tens of millions of people worldwide:

- Onchocerciasis: the Role of Wolbachia Bacterial Endosymbionts in Parasite Biology, Disease Pathogenesis, and Treatment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131055/
- The Role of Endosymbiotic Wolbachia Bacteria in the Pathogenesis of River Blindness http://www.nature.com/news/2002/020304/full/news020304-9.html
- Short Course, High Dose Rifampicin Achieves Wolbachia Depletion Predictive of Curative Outcomes in Preclinical Models of Lymphatic Filariasis and Onchocerciasis http://archive.lstmed.ac.uk/6918/
- Wolbachia bacteria in filarial immunity and disease. https://www.ncbi.nlm.nih.gov/pubmed/11472559

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2. **Feedback to Comments in EPA's Response to Comments Received on the April 26, 2016, Notice of Receipt for an Amendment and Extension to Experimental Use Permit 88877-EUP-2 (Docket ID Number: EPA-HQ-OPP-2015-0374; FRL-9944-96) cited in the email.** EPA's response to comments Public Comment #3.

**EPA Response to Public Comment #2** – *"The Wolbachia-based Aedes aegypti product proposed for experimental field trials mimics the cytoplasmic incompatibility phenotype as known from numerous insects and other arthropods; while a single report exists in the literature indicating natural infection of Aedes aegypti, it is estimated that greater than 1 million species extant in the environment harbor naturally occurring Wolbachia strains. This presence and degree of exposure to a variety of organisms without documented negative impacts suggests that the product under consideration by EPA is also likely to pose minimal probability of adverse effects to humans and the environment."*

**Feedback** - This seems to state the following:

1. There are "naturally occurring" *Wolbachia* in over 1 million species "without documented negative impacts," therefore, *Wolbachia* in Aedes aegypti is "likely to pose" minimal risk; and
2. *Wolbachia* strains associated with River Blindness and lympatic filariasis have been well documented, yet they are different to the *Wolbachia* strain being utilized, so there should be no risk.

These points are logically inconsistent and are mutually incompatible. On the one hand, this comment says there are no risks because of no documented negative effects. Yet there are obviously negative documented negative effects, yet these don't count.

These publications discuss *Wolbachia's* association with devastating diseases that impact tens of millions of people worldwide, as well as its potential role in driving pathogen increase in its hosts:

- Onchocerciasis: the Role of Wolbachia Bacterial Endosymbionts in Parasite Biology, Disease Pathogenesis, and Treatment
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131055/
- The Role of Endosymbiotic Wolbachia Bacteria in the Pathogenesis of River Blindness
  http://www.nature.com/news/2002/020304/full/news020304-9.html
- Wolbachia bacteria in filarial immunity and disease.
  https://www.ncbi.nlm.nih.gov/pubmed/11472559
- Short Course, High Dose Rifampicin Achieves Wolbachia Depletion Predictive of Curative Outcomes in Preclinical Models of Lymphatic Filariasis and Onchocerciasis
  http://archive.lstmed.ac.uk/6918/
- Wolbachia Can Enhance Plasmodium Infection in Mosquitoes: Implications for Malaria Control?
  http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004182
- Wolbachia Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis
  http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965
- Wolbachia increases susceptibility to Plasmodium infection in a natural system
  http://rspb.royalsocietypublishing.org/content/281/1779/20132837
- Wolbachia Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
- Wolbachia in a major African crop pest increases susceptibility to viral disease rather than protects.
  https://www.ncbi.nlm.nih.gov/pubmed/22731846

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**EPA Response to Public Comment #2** – *"...it is estimated that greater than 1 million species extant in the environment harbor naturally occurring Wolbachia strains. This presence and degree of exposure to a variety of organisms without documented negative impacts suggests that the product under consideration by EPA is also likely to pose minimal probability of adverse effects to humans and the environment."*

**Feedback** – All *Wolbachia* are not created equal, yet those that wish to see it used as a vector control method consistently note that up to ~60% of insects (some estimates of *Wolbachia* penetration are significantly lower) may be infected with it.

The fact they are not equal is supported by the fact that teams interested in *Wolbachia* as a vector control method tested several different *Wolbachia* strains in *Aedes* to get to one that

gave the desired lethality in offspring. Some strains gave no lethality at all, and other strains resulted in less than desired lethality.

More importantly, when *Wolbachia*-infected filarial worms invade the human body through the bites of insects, namely mosquitoes and flies, human immune responses occur which lead to river blindness and lymphatic filariasis that impact the lives of tens of millions of people across the globe. Here are some of the publications that cover *Wolbachia* and these diseases:

- Onchocerciasis: the Role of Wolbachia Bacterial Endosymbionts in Parasite Biology, Disease Pathogenesis, and Treatment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131055/
- The Role of Endosymbiotic Wolbachia Bacteria in the Pathogenesis of River Blindness http://www.nature.com/news/2002/020304/full/news020304-9.html
- Wolbachia bacteria in filarial immunity and disease. https://www.ncbi.nlm.nih.gov/pubmed/11472559
- Short Course, High Dose Rifampicin Achieves Wolbachia Depletion Predictive of Curative Outcomes in Preclinical Models of Lymphatic Filariasis and Onchocerciasis http://archive.lstmed.ac.uk/6918/

Therefore, the logic that the *"presence and degree of exposure to a variety of organisms without documented negative impacts suggests that the product under consideration by EPA is also likely to pose minimal probability of adverse effects to humans and the environment"* should be reconsidered as it is not clear that statement is accurate, especially with respect to these flies and mosquitoes that are the source for the widespread river blindness and lymphatic filariasis diseases.

In the case of wAlbB specifically, what percentage of insects have been infected with it? There are documented cases of this bacterium driving pathogen production higher in the hosts it invades including those listed below that are (1) specific to mosquitoes and (2) also involve the wAlbB strain of *Wolbachia*:

- *Wolbachia* Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
- *Wolbachia* Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965

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**EPA Response to Public Comment #2** – *"...while a single report exists in the literature indicating natural infection of Aedes aegypti"*

**Feedback** –The report that is cited in the EPA response links to a NCBI Taxonomy page (here).

There is another paper that was published in 2009 (Klasson et al) that raises concerns regarding natural infection of *Aedes aegypti*:

- Horizontal gene transfer between *Wolbachia* and the mosquito Aedes aegypti https://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-10-33

Here is excerpt from this paper by Klasson et al:

- "We have discovered a case of horizontal gene transfer (HGT), involving two adjacent genes, between the genomes of *Wolbachia* and the currently *Wolbachia*-uninfected mosquito Aedes aegypti, an important human disease vector. The lower level of sequence identity between *Wolbachia* and insect, the transcription of all the genes involved, and the fact that we have identified homologs of the two genes in another Aedes species (Ae. mascarensis), suggest that these genes are being expressed after an extended evolutionary period since horizontal transfer, and therefore that the transfer has functional significance. The association of these genes with *Wolbachia* prophage regions also provides a mechanism for the transfer. The data support the argument that HGT between *Wolbachia* endosymbiotic bacteria and their hosts has produced evolutionary innovation."

Given this publication has unknown implications regarding artificially inserting *Wolbachia* back into *Aedes aegypti*, has EPA been provided test data or other evidence that substantiates or negates its conclusions?

Of note in the 2016 publication by Bordenstein cited earlier - Eukaryotic association module in phage WO genomes from Wolbachia http://www.nature.com/articles/ncomms13155 - the authors stated *'Among this subset with eukaryotic sequence homology, the protein domains are almost exclusively found in the phage eukaryotic association module (EAM). An EAM has never before been reported in bacteriophage genomes, to our knowledge, possibly because phages of obligate intracellular bacteria occupy a unique eukaryotic-enclosed niche and are relatively understudied'.*

This is an important observation, along with other evidence of HGT that indicates there is still a lot to understand about the interaction of *Wolbachia* with its host and the implications.

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**EPA Response to Public Comment #3 –** *"The wAlbB Aedes aegypti strain is not intended to affect the competency of the vector to transmit viral agents. Currently, there is no compelling evidence that wAlbB in Aedes aegypti does affect the capacity of the vector to transmit disease agents."*

**Feedback –** Has the vector competency work been completed to establish this? As the EPA comment highlighted, it is known that '*Wolbachia causes very different responses*

*depending on the host',* so any new *Wolbachia* host interaction should be fully investigated including any change in disease vectoring capacity which these publications suggest occurs:

- Wolbachia Can Enhance Plasmodium Infection in Mosquitoes: Implications for Malaria Control?
  http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004182
- Wolbachia Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis
  http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965
- Wolbachia increases susceptibility to Plasmodium infection in a natural system
  http://rspb.royalsocietypublishing.org/content/281/1779/20132837
- Wolbachia Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
- Wolbachia in a major African crop pest increases susceptibility to viral disease rather than protects.
  https://www.ncbi.nlm.nih.gov/pubmed/22731846

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**EPA Response to Public Comment #3** – *"Even with this strategy of deliberate male and female releases, failure to establish Wolbachia-infected populations has occurred in some instances."*

**Feedback** – This reference to "failure to establish *Wolbachia*-infected populations" occurring in "some instances" is based on a different clade of *Wolbachia* known as wMel from D melanogaster, whereas MosquitoMate uses a wAlbB strain from Aedes albopictus. With this in mind, have there been tests done to show it will not happen specific to the CI approach with wAlbB *Wolbachia* in Aedes aegypti?

This is relevant given the entire strategy depends on not releasing infected females, and the consequences are failure of the approach to control the *Aedes aegypti* population and the spreading of a bacterium into the environment in a human biting mosquito with unknown potential adverse effects.

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**EPA Response to Public Comment #3** – *"Establishing a wAlbB Aedes aegypti population is highly unlikely because only males are released with very few potential accidental female releases, i.e., less than 1 female per 250,000 males (U.S. EPA, 2015a and 2015b)."*

**Feedback** – This equation results in a 99.9996% sex sorting ratio. Publications show sex sorting efficiency in mosquitoes range from 96-99.99%, with some approaches as low as 85% (http://johnwhock.com/wp-content/uploads/2012/09/instr_5412_separator.pdf).

With a proprietary approach Oxitec has achieved 99.99% efficiency at scale. What scale is this reported 99.9996% sex sorting ratio achieved? Is this based on releases of thousands or millions of mosquitoes? Are there validated data demonstrating this level of efficiency that are publicly available? We are aware of no published data showing this sorting efficiency that has been afforded independent review.

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**EPA Response to Public Comment #3** – *"According to Xi et al. (2005), in caged releases of wAlbB Aedes aegypti females with uninfected males, a minimum of 20% of females needed to be released to establish the Wolbachia infection after seven generations. All releases below 20% in that cage experiment resulted in failure of the wAlbB infection to be established in the population."*

**Feedback**: The Xi et al (2005) paper were very small cage trials (100 adults per cage) and do not reflect conditions in the field. Additionally as noted in the EPA response, the Xi et al study did not test for the unintentional release of wAlbB females right next to wAlbB males in the environment, but rather wAlbB females into a population of uninfected males in cages. Given the compatibility between infected wAlbB males and wAlbB females, a single female release could theoretically lead to the persistence of *Wolbachia* in subsequent generations of *Aedes aegypti*.

The entire strategy employed by MosquitoMate depends on not releasing females, and the risk of accidental female release has not been fully assessed. This could result in a failure of the technology to control the *Aedes aegypti* population, and lead to the spread of a bacterium that is not fully understood into the environment and into a pervasive human biting mosquito.

Furthermore, understanding what happens in naturally in the environment with respect to the spread of *Wolbachia* is worthy of consideration as opposed to small cage trial results that tested for something completely different than the risk of accidental releases of wAlbB females alongside compatible wAlbB males. Notably, it is impossible that when *Wolbachia* invades a population it does so by infecting over 20% of that population at one time. It starts with a few individuals that somehow get infected with *Wolbachia* (there is still a lot of debate as to how *Wolbachia* spreads between species) and then it spreads through the entire population over time.

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**EPA Response to Public Comment #3** – *"It may be possible to establish a wAlbB Aedes aegypti population with use of the wAlbB strain. This, however, would only be possible if substantial numbers of females were released into an ecosystem along with repeated male wAlbB Aedes aegypti releases. The release of females is strictly controlled in the quality*

*control procedures during mechanical separation of pupae and microscopic inspection of sorted pupae (U.S. EPA, 2015a)."*

**Feedback –** The risk of releasing females increases with the scale of deployment. What are the QC checks in place and can they be scaled reliably? We know of no published data independently validating the sorting efficiency for this strain. As the consequences of female releases are unknown (Will it spread under field conditions? What happens if it spreads? Can it affect vectorial capacity?), the sorting efficiency is of paramount importance and therefore requires utmost scrutiny and validation.

Additionally please see previous response regarding assumption that the establishment of a *w*AlbB *Aedes aegypti* population is only possible "if substantial numbers of females were released into an ecosystem". This is an assumption based on 5 small cage trials and is not consistent or relevant to how *Wolbachia* naturally invades a species.

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**EPA Response to Public Comment #3** – *"In addition, UKDE monitors the environment near its rearing facilities for inadvertent release or escape of female Aedes aegypti wAlbB. As with any mechanical separation technique for mosquitoes, continual monitoring and quality assurance measures are paramount for ensuring that only males are released."*

**Feedback** - How is this accomplished? What sorts of assay are used with what accuracy, and what are the limits of detection? What do you do if you find female *Aedes aegypti* infected with wAlbB?

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**EPA Response to Public Comment #3** – *"Currently, there is no compelling evidence that wAlbB in Aedes aegypti does affect the capacity of the vector to transmit disease agents. A few published manuscripts have discussed West Nile virus (WNV) and Plasmodium titers increasing in Wolbachia-positive strains, but Aedes aegypti are not a natural malaria vector and Aedes aegypti do not generally carry WNV (Hughes et al., 2014a). Because Aedes aegypti are not a natural malaria vector, research showing the effects in Culex pipiens cannot be used to assume this is true for Aedes aegypti. Additionally, Hughes et al. (2012) discusses Plasmodium infections in Anopheles gambiae with wAlbB, and this is not applicable to the situation with Aedes aegypti."*

**Feedback** – As highlighted in the EPA comment '*Wolbachia causes very different responses depending on the host*', therefore every insertion of *Wolbachia* into a new host, as is the case with *Aedes aegypti*, should be fully assessed and tested especially if the interactions are unknown and unpredictable. Have biosafety tests been run by the applicant to confirm wAlbB in *Aedes aegypti* does not affect the capacity of the vector to increase pathogen

production and transmit disease agents as various publications suggest?

This is an important question when the following publications that show *Wolbachia* can increase viral load in its hosts are taken into consideration:

- Wolbachia Can Enhance Plasmodium Infection in Mosquitoes: Implications for Malaria Control?
  http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004182
- Wolbachia Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis
  http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965
- Wolbachia increases susceptibility to Plasmodium infection in a natural system
  http://rspb.royalsocietypublishing.org/content/281/1779/20132837
- Wolbachia Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
- Wolbachia in a major African crop pest increases susceptibility to viral disease rather than protects.
  https://www.ncbi.nlm.nih.gov/pubmed/22731846

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**EPA Response to Public Comment #5** – *"The likelihood of wAlbB Aedes aegypti survival is considered low given that males are dead end hosts, the small number of potential accidental female releases, and bidirectional cytoplasmic incompatibility. As mentioned in the Response to Public Comment #3, at least 20% of the population of females would need to be released to establish a wAlbB Aedes aegypti constant population."*

**Feedback** – Males are dead end hosts only when sex-sorting is 100%. Notably any *Wolbachia* female mosquitoes released will be pre-mated (as adults are released that are over 2 days old), mature, ready to feed on human hosts, and lay eggs that can survive to adulthood.

With respect to the *"at least 20% of the population of females would need to be released to establish a wAlbB Aedes aegypti constant population",* as mentioned earlier the Xi et al (2005) paper were very small cage trials (100 adults per cage) and do not reflect conditions in the field. Additionally, as noted in the EPA response, the Xi et al study did not test for the unintentional release of wAlbB females right next to wAlbB males, but rather wAlbB females into a population of uninfected males in cages. Given the compatibility between infected wAlbB males and wAlbB females, a single female release could theoretically lead to the persistence of *Wolbachia* in subsequent generations of Aedes aegypti.

The entire strategy employed by MosquitoMate depends on not releasing females, and the risk of accidental female release has not been fully assessed. This could result in a complete failure of the technology to control the *Aedes aegypti* population, and lead to the spread of

a bacterium that is not fully understood into the environment via a pervasive human biting mosquito.

Furthermore, understanding what happens in naturally in the environment with respect to the spread of *Wolbachia* is worthy of consideration as opposed to small cage trial results that tested for something completely different than the risk of accidental releases of wAlbB females alongside compatible wAlbB males. Notably, it is impossible that when *Wolbachia* invades a population it does so by infecting over 20% of that population at one time. It starts with a few individuals that somehow get infected with *Wolbachia* (there is still a lot of debate as to how *Wolbachia* spreads between species) and then it spreads through the entire population over time.

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**EPA Response to Public Comment #7** – *"As discussed in Brelsfoard and Dobson (2009), in Drosophila melanogaster, the wMel strain of Wolbachia may influence the susceptibility of this fly to RNA-type viruses. It is further hypothesized that this phenomenon may occur in other host species harboring Wolbachia; however, no direct evidence is provided. Aedes aegypti reared by UKDE for release of Wolbachia-infected males are checked for the presence of infectious virus particles as part of the manufacturing process. Any significant changes that may occur with respect to favoring the presence of a pathogen would therefore be noted as part of the quality assurance protocols in place."*

**Feedback** – Checking for the presence of the virus in a facility where the females are kept in cages and have limited exposure to human viruses (such as Zika, dengue, chikungunya, yellow fever etc.) is not a test for influences on susceptibility.

Has the potential phenomenon of *Wolbachia* impacting susceptibility of RNA-type viruses to hosts such as flies been specifically tested in the *Wolbachia* wAlbB strain of *Aedes aegypti* mosquitoes?

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**EPA Response to Public Comment #7** – *"Calvitti et al. (2015) showed that wAlbA Aedes albopictus in dense rearing conditions did not decrease the cytoplasmic incompatibility (CI) effect. Islam and Dobson (2006) also showed that rearing Aedes albopictus with Wolbachia under crowded, low food conditions did not impact the CI effect. Yamada et al. (2007) cited by Oxitec, Ltd. refers to the effect in Drosophila, not mosquitoes."*

**Feedback** - *Aedes albopictus* has adapted to the presence of wAlbA/B over a long period of time, whereas *Aedes aegypti* has only recently been infected with wAlbB. Hence the example from Yamada et al (2007) is relevant because it suggests that a similar effect may occur in *Aedes aegypti* – that is that males that developed faster had almost complete cytoplasmic incompatibility (CI) whereas those that developed more slowly lost much of the

CI effect. This should be tested for and evaluated properly in *Aedes aegypti* under a range of different rearing conditions and male development time; otherwise there is a risk of releasing males with incomplete CI causing a failure to control the *Aedes aegypti* mosquito population.

---

In summary, examining these biosafety risks with this strain, in this species of mosquito, and with the relevant disease vectors is a completely possible thing to do. To require that an applicant have done so, prior to being approved for field trials, is not only reasonable but a necessary standard.

This should especially be required in a case, as we have here, in which so many serious scientific journal articles attest to significant risks to human health posed by *Wolbachia*, in other human biting insects and with a variety of disease causing organisms.

Message

**From:** Jain, Komal [Komal_Jain@americanchemistry.com]
**Sent:** 8/4/2017 6:34:47 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** hiring?

Hi Nancy,

I hope you are doing well. Busy for sure! I'd love to catch up whenever you can clear your calendar for lunch or a cocktail.

I heard through Seth Goldberg that you may be hiring for several positions. I'm not inquiring for myself, but for my husband Craig who has been in the environmental arena for a long time. In fact, he is a former EPA employee; he was with the Energy Star program for several years. He recently left Toshiba where he ran its environmental affairs program for the Americas for 10+ years. He's looking for senior level position in a policy/management role (not a scientist). Anything come to mind? I can shoot his CV over if there is a possibility.

Thanks! And, Happy Friday.

All the best,
Komal

*Komal K. Jain, J.D.* | American Chemistry Council
Senior Director, Chemical Products & Technology Division
komal_jain@americanchemistry.com
700 2nd Street, NE | Washington, DC | 20002
o: Ex. 6
m: Ex. 6

Message

**From:** Jain, Komal [Komal_Jain@americanchemistry.com]
**Sent:** 8/7/2017 8:51:18 PM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** RE: hiring?
**Attachments:** Ex. 6 U.S. EPA_resume.docx

**Flag:** Flag for follow up

Thanks so much Nancy. See attached

A few quick highlights:

- Ex. 6

Best, Komal

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, August 4, 2017 2:53 PM
**To:** Jain, Komal <Komal_Jain@americanchemistry.com>
**Subject:** RE: hiring?

Ok. definitely send a CV. There is a hiring freeze (unless he wants to be a fellow ☺) so I think political is the most workable.

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Jain, Komal [mailto:Komal_Jain@americanchemistry.com]
**Sent:** Friday, August 4, 2017 2:45 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** RE: hiring?

He would certainly consider it.

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, August 4, 2017 2:38 PM
**To:** Jain, Komal <Komal_Jain@americanchemistry.com>
**Subject:** RE: hiring?

Hey Komal,
Would he take a political position?

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Jain, Komal [mailto:Komal_Jain@americanchemistry.com]
**Sent:** Friday, August 4, 2017 2:35 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** hiring?

Hi Nancy,

I hope you are doing well. Busy for sure! I'd love to catch up whenever you can clear your calendar for lunch or a cocktail.

I heard through Seth Goldberg that you may be hiring for several positions. I'm not inquiring for myself, but for Ex. 6 Ex. 6 who has been in the environmental arena for a long time. In fact, he is Ex. 6 Ex. 6 Ex. 6 He's looking for senior level position in a policy/management role (not a scientist). Anything come to mind? I can shoot his CV over if there is a possibility.

Thanks! And, Happy Friday.

All the best,
Komal

*Komal K. Jain, J.D.* | American Chemistry Council
Senior Director, Chemical Products & Technology Division
komal_jain@americanchemistry.com
700 2nd Street, NE | Washington, DC | 20002
o: Ex. 6
m: Ex. 6


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therefore does not accept liability for any errors or omissions in the contents of this message which arise as a result of email transmission. American Chemistry Council, 700 – 2nd Street NE, Washington, DC 20002, www.americanchemistry.com
++++++++++++++++++++++++++++++ This message may contain confidential information and is intended only for the individual named. If you are not the named addressee do not disseminate, distribute or copy this email. Please notify the sender immediately by email if you have received this email by mistake and delete this email from your system. E-mail transmission cannot be guaranteed to be secure or error-free as information could be intercepted, corrupted, lost, destroyed, arrive late or incomplete, or contain viruses. The sender therefore does not accept liability for any errors or omissions in the contents of this message which arise as a result of email transmission. American Chemistry Council, 700 – 2nd Street NE, Washington, DC 20002, www.americanchemistry.com

Message

**From:** Roy Bailey [rbailey@gdcillc.com]
**Sent:** 8/18/2017 2:27:12 AM
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC:** Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]
**Subject:** Re: For your assistance

Nancy,

Thanks so much for your response. I do really appreciate it.

As I understand it, others like Intrexon have already done lengthy research to determine and prove that there is absolutely NO human or environmental impact with their technology application. This was done way before being allowed or considered for field trials.

We just want the same standards applied across the board. It's not too much to ask when it comes to the possible consequences for mankind.

Please know that we will be more than happy to meet with your team of scientists to discuss if helpful.

Have a great weekend.

Best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Aug 17, 2017, at 6:13 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Roy,
> I think the important thing to keep in mind that the standards for an EUP (which is what was approved for the Wolbachia) are more lenient than those for a full section 3 registration. The EUP allows for the collection of information that would then be used to inform a full registration. Nevertheless, I should have further details back from staff early next week and would be happy to chat after that.
>
> Regards,
> Nancy
>
> ---
> Nancy B. Beck, Ph.D., DABT

Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Roy Bailey [mailto:rbailey@gdcillc.com]
**Sent:** Wednesday, August 9, 2017 10:59 AM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Cc:** Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>
**Subject:** Re: For your assistance

Nancy,

Good morning, hope all is well.

I am just checking in to see where we stand on our request. How can we assist ? Happy to meet with your team if helpful.

All my best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Jul 28, 2017, at 4:33 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Thanks Roy.
> I will pass these along to our experts for their review and input. I will get back to you once I have a sense from them regarding how long a review will take.
>
> Regards,
> Nancy
>
> ---
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> **From:** Roy Bailey [mailto:rbailey@gdcillc.com]
> **Sent:** Friday, July 28, 2017 5:17 PM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** Roy Bailey <rbailey@gdcillc.com>
> **Subject:** For your assistance

Nancy,

Please find the attachment for you and the team's review. It is a thoughtful and substantive summary of answers and feedbacks to that which was sent to me earlier this week.

I hope you all find this helpful. We are more than happy to get together next week or whenever you think appropriate.

All my respect and regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

> **From:** "Chris Basta (INTREXON CORP)" <cbasta7@bloomberg.net>
> **Date:** July 28, 2017 at 3:49:10 PM CDT
> **To:** undisclosed-recipients:;
> **Subject: Follow-up**
> **Reply-To:** Chris Basta <cbasta7@bloomberg.net>
>
> Roy,
>
> With respect to the email you had sent on Tuesday regarding the scientific
> publications highlighting concerns or risks surrounding Wolbachia, please see
> the attached document with feedback to the points that were raised.
>
> Hope you have a great weekend.
>
> Best regards,
> Chris

Message

**From**: Roy Bailey [rbailey@gdcillc.com]
**Sent**: 7/21/2017 10:24:07 PM
**To**: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
**CC**: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject**: Re: Revised memo

I'm just checking in - any update ?

Have a great weekend

BTW, I will be with RJ Kirk of Intrexon in DC on Wed for meetings w Sec Perry of DOE. Happy to swing by if you need anything.

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Jul 19, 2017, at 6:39 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:

> Haven't forgotten you. Will touch base this Friday.
>
> Sent from my iPhone
>
> On Jul 16, 2017, at 8:42 PM, Roy Bailey <rbailey@gdcillc.com> wrote:
>
> > Thanks so much Tate
> >
> > Roy W. Bailey
> > CEO
> > Giuliani Deason Capital Interests, LLC
> > Cell Ex. 6
> > Office Ex. 6
> > Rbailey@gdcillc.com
> > Rbailey@baileystrategicadvisors.com
> >
> > On Jul 16, 2017, at 6:02 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:
> >
> > > Thanks Roy- again, we will definitely follow up on the staff level.
> > >
> > > Sent from my iPhone
> > >
> > > On Jul 16, 2017, at 6:29 PM, Roy Bailey <rbailey@gdcillc.com> wrote:

Administrator,

I have attached a revised memo which we think may be even more compelling and helpful. ( sorry that it wasn't included in the previous email. ) We are available for a call anytime today or tomorrow that is convenient for your team.

Again, we hope the EPA will consider revoking the field trial permit EUP for the referenced technology until the EPA can complete a full impact study on humans and the environment.

Thanks for your interest and consideration.

Respectfully and best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

**From:** "Bobo, Jack" <JBobo@intrexon.com>
**Date:** July 16, 2017 at 3:07:45 PM PDT
**To:** 'Roy Bailey' <rbailey@gdcillc.com>
**Subject: EPA Memo Updated**

---

any purpose. Thank you for your cooperation.

<EPA Improperly Granted the Wolbachia EUP_07 16 17.docx>

Message

**From**: Roy Bailey [rbailey@gdcillc.com]
**Sent**: 7/28/2017 2:31:26 PM
**To**: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC**: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]; Gay Ludwick [gay@gdcillc.com]
**Subject**: Re: Wolbachia doc

Nancy

That certainly makes sense, thanks much. I will send you a thorough analysis in the next few days.

All my best

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Jul 28, 2017, at 9:11 AM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Roy,
> Thanks for the heads up. It would probably make sense for the OPP experts to take a look at what will send and digest it a bit before we have a follow-up meeting. Next Tuesday/Wednesday may be a bit too soon, but we can make that call once we have more materials from you.
>
> Regards,
> Nancy
>
> ---
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> **From:** Roy Bailey [mailto:rbailey@gdcillc.com]
> **Sent:** Friday, July 28, 2017 9:02 AM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>; Gay Ludwick <gay@gdcillc.com>
> **Subject:** Re: Wolbachia doc
>
> Nancy,

Thanks so much for the responses. There remain serious concerns and I will send you a more substantive reply later today or by the weekend latest.

We will be in DC next week on Tues and Wed and would be happy to sit down to discuss details if helpful. Please let me know.

All my sincere regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Jul 25, 2017, at 11:04 AM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Roy,
> Thank you for sending this information.
> In response to your comments, our staff checked on whether these concerns were addressed in the response to comments document that was issued August 30 2016.
> An overview of responses is below:
>
> Citations 1, 2, 3, 4, and 6: Addressed in EPA's response to comments Public Comment #3.
>
> Citation 5: This research is for a completely different organism, *Spodoptera exempta* (African armyworm), not mosquitoes, and *Wolbachia* causes very different responses depending on the host. This information, while interesting, cannot be used to make predictions about mosquitoes.
>
> Citation 7: Addressed in EPA's response to comments Public Comment #4.
>
> Citations 8, 9, 10, and 11: Addressed in EPA's response to comments Public Comment #7.
>
> Citation 12: With respect to the *Wolbachia* phage encoding a toxin from the black widow spider, this comment is referring to Citation 12 ("Eukaryotic association module in phage WO genomes from *Wolbachia*"). In this study, the WO-B phage in *w*AlbB strain mosquitoes were not studied. Only moth and parasitoid wasp WO phage were researched. *Aedes aegypti w*AlbB strain does have a WO-B phage associated with it; however, phage are specific to their hosts, horizontal gene transfer is happening on evolutionary time scales, there is no indication that the widow spider toxin sequence is expressed in the *Wolbachia* infection, and it is not reported that the WO-B phage in *w*AlbB *Aedes aegypti* produce the toxin from black widow spider. Also, most importantly, viruses have been shown to incorporate host sequences numerous times, but this is the first report of a virus of an obligate intercellular parasitic bacterium having sequences from both hosts: bacterial and eukaryotic. The widow spider toxin is a huge multimeric toxin with

the entire 150kD monomer needing to be expressed and binding to form a tetramer to have full toxin activity. The sequence detected in the prophage sequence is only the C-terminus (maybe 18 kD) of the entire monomeric protein (150 kD). This C-terminus has been implicated in passage through membranes to release the toxins when produced in the spider. Furthermore, there is no evidence that *Wolbachia* alone are being transferred to animals when a female mosquito bites and takes a blood meal from an animal.

Citation 13, 14, and 15: The *Wolbachia pipientis* strains associated with River blindness and lymphatic filariasis are in different clades than the *w*AlbB, and the *w*AlbB strain is not associated with these diseases.

If there are still concerns that you are worried are not adequately addressed, I'm sure we can get our scientific experts together for further discussions.

Regards,
Nancy

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
Ex. 6
beck.nancy@epa.gov

**From:** Roy Bailey [mailto:rbailey@gdcillc.com]
**Sent:** Sunday, July 16, 2017 1:39 PM
**To:** Bennett, Tate <Bennett.Tate@epa.gov>; Brown, Byron <brown.byron@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
**Cc:** Roy Bailey <rbailey@gdcillc.com>; Gay Ludwick <gay@gdcillc.com>
**Subject:** Fwd: Wolbachia doc

Tate,

This additional info may be helpful as well. Thanks so much for your call and attention to the concerns.

Best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

> **From:** "Basta, Christopher" <CBasta@intrexon.com>
> **Date:** July 16, 2017 at 10:22:45 AM PDT
> **To:** Roy Bailey <rbailey@gdcillc.com>

**Cc:** "Kirk, Randal J" <RJ.Kirk@intrexon.com>, "Bobo, Jack" <JBobo@intrexon.com>
**Subject: Wolbachia doc**

Roy,

RJ asked that I send you this document that provides a Wolbachia overview as well as a list of publications that cover various Wolbachia concerns & potential issues.

Best,
Chris

**Christopher Basta**
Vice President, Investor Relations
**Intrexon Corporation**
Work: Ex. 6
Cell: Ex. 6
www.dna.com



<Wolbachia Overview and Publications Citing Concerns and Risks.docx>

Message

**From**: White, Kimberly [Kimberly_White@americanchemistry.com]
**Sent**: 8/16/2017 8:38:21 PM
**To**: Goldstein, Bernard D [bdgold@pitt.edu]; Terry F. Yosie [tyosie@wec.org]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Joe Arvai [jlarvai@umich.edu]; rdenison@edf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b2358277ea84ca2a4375a8b8744a7af-rdenison@edf.org]
**Subject**: RE: SRA 2017 Annual Meeting Roundtable Acceptance

Thanks for the update Bernie and looking forward to the session discussion.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: Ex. 6 C: Ex. 6
www.americanchemistry.com

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Wednesday, August 16, 2017 8:13 AM
**To:** Terry F. Yosie; White, Kimberly; Beck, Nancy; Joe Arvai; Richard Denison
**Subject:** FW: SRA 2017 Annual Meeting Roundtable Acceptance

Congratulations to us all. We are on the schedule for Tuesday afternoon, 12/12, from 1:30-3pm.

Just as a reminder:. The final order of presentations is open – it will be ten minutes each except for Terry who is our MC. Should leave 40 min for discussion. Again, the focus should be on the optimal principles and how best to achieve them rather than a critique of specific legislation. Our abstract is below

*Recent activities by both Congress and by EPA Administrator Pruitt provide an opportunity to evaluate approaches for organizing risk-related scientific advisory processes for regulatory agencies. The EPA Science Advisory Board Reform Act has been passed by the US House of Representatives and is awaiting action in the US Senate, which may or may or may not be forthcoming. These have generated media interest and controversy and some have characterized these actions as unnecessarily politicizing science and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes. Others have pointed out that there is a need to broaden scientific representation in diverse fields, and to improve procedures for balancing perspectives and perceived biases on EPA scientific advisory panels. The Roundtable participants will be asked to focus on the underlying principles that should guide the science advisory processes for the optimal provision of scientific advice on risk-related issues to a regulatory agency.*

Hope you are all having a good summer

Bernie

# Subject: SRA 2017 Annual Meeting Roundtable Acceptance

What is the Optimal Approach to Organizing Governmental Risk-Related Science Advisory Processes

has been accepted for the 2017 Meeting in Arlington, VA on

10-14 December as a

**Roundtable Session**

on Tuesday, December 12, from 1:30 PM to 3:00 PM. The online program will be available by August 15. You will be able to view it by going to http://sra.org/events/sra-2017-annual-meeting

Please note that all persons attending the Annual Meeting (or any part thereof) are **REQUIRED** to pay the appropriate registration fee as indicated on the registration form. Most importantly, **ALL PRESENTERS IN YOUR ROUNTABLE SESSION MUST REGISTER FOR THE MEETING.** (Registration will open at the end of August at www.SRA.org.) If for any reason you need to cancel your presentation, as a courtesy to the Society and the other meeting participants, please contact your session chair, the Annual Meeting Committee chair (Terje Aven, terje.aven@uis.no), AND Jennifer Rosenberg of the SRA Secretariat (jrosenberg@burkinc.com) as soon as possible.

Please upload all Powerpoint presentations for your session by December 4 at http://burkinc.net/sraAM/index.php3. Instructions for the upload of your presentation will be posted at www.sra.org after 30 September. It is very important that you follow these instructions and upload before the meeting so the session will run smoothly.

Please go to www.sra.org to view the preliminary program and information for registering for the meeting (which will be posted soon). A room block has been set aside at the Crystal Gateway Marriott. Reservations can be made at the special SRA rate by using this link - https://aws.passkey.com/event/49022912/owner/1487/home

Thank you for your participation. We look forward to seeing you in Arlington in December.

Terje Aven

SRA President-Elect and Annual Meeting Chair

Jennifer Rosenberg

Director, Meetings and Events

Jennifer Rosenberg, CMP
Director, Meetings and Events
1313 Dolley Madison Blvd.
Suite 402
McLean VA 22101
703-790-1745 Ex. 6
Fax: 703-790-2672
jrosenberg@burkinc.com

Message

**From:** Terry F. Yosie [tyosie@wec.org]
**Sent:** 8/16/2017 6:25:42 PM
**To:** Goldstein, Bernard D [bdgold@pitt.edu]
**CC:** White, Kimberly [Kimberly_White@americanchemistry.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Joe Arvai [jlarvai@umich.edu]; rdenison@edf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b2358277ea84ca2a4375a8b8744a7af-rdenison@edf.org]; Terry F. Yosie [tyosie@wec.org]
**Subject:** Re: SRA 2017 Annual Meeting Roundtable Acceptance

Thanks Bernie. This time frame works for me.

Terry

Sent from my iPhone

On Aug 16, 2017, at 2:12 PM, Goldstein, Bernard D <bdgold@pitt.edu> wrote:

> Congratulations to us all. We are on the schedule for Tuesday afternoon, 12/12, from 1:30-3pm.
>
> Just as a reminder:. The final order of presentations is open – it will be ten minutes each except for Terry who is our MC. Should leave 40 min for discussion. Again, the focus should be on the optimal principles and how best to achieve them rather than a critique of specific legislation. Our abstract is below
>
> *Recent activities by both Congress and by EPA Administrator Pruitt provide an opportunity to evaluate approaches for organizing risk-related scientific advisory processes for regulatory agencies. The EPA Science Advisory Board Reform Act has been passed by the US House of Representatives and is awaiting action in the US Senate, which may or may or may not be forthcoming. These have generated media interest and controversy and some have characterized these actions as unnecessarily politicizing science and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes. Others have pointed out that there is a need to broaden scientific representation in diverse fields, and to improve procedures for balancing perspectives and perceived biases on EPA scientific advisory panels. The Roundtable participants will be asked to focus on the underlying principles that should guide the science advisory processes for the optimal provision of scientific advice on risk-related issues to a regulatory agency.*
>
> Hope you are all having a good summer
>
> Bernie

# Subject: SRA 2017 Annual Meeting Roundtable Acceptance

What is the Optimal Approach to Organizing Governmental Risk-Related Science Advisory Processes

has been accepted for the 2017 Meeting in Arlington, VA on

10-14 December as a

**Roundtable Session**

on Tuesday, December 12, from 1:30 PM to 3:00 PM. The online program will be available by August 15. You will be able to view it by going to http://sra.org/events/sra-2017-annual-meeting

Please note that all persons attending the Annual Meeting (or any part thereof) are **REQUIRED** to pay the appropriate registration fee as indicated on the registration form. Most importantly, **ALL PRESENTERS IN YOUR ROUNTABLE SESSION MUST REGISTER FOR THE MEETING.** (Registration will open at the end of August at www.SRA.org.) If for any reason you need to cancel your presentation, as a courtesy to the Society and the other meeting participants, please contact your session chair, the Annual Meeting Committee chair (Terje Aven, terje.aven@uis.no), AND Jennifer Rosenberg of the SRA Secretariat (jrosenberg@burkinc.com) as soon as possible.

Please upload all Powerpoint presentations for your session by December 4 at http://burkinc.net/sraAM/index.php3. Instructions for the upload of your presentation will be posted at www.sra.org after 30 September. It is very important that you follow these instructions and upload before the meeting so the session will run smoothly.

Please go to www.sra.org to view the preliminary program and information for registering for the meeting (which will be posted soon). A room block has been set aside at the Crystal Gateway Marriott. Reservations can be made at the special SRA rate by using this link - https://aws.passkey.com/event/49022912/owner/1487/home

Thank you for your participation. We look forward to seeing you in Arlington in December.

Terje Aven

SRA President-Elect and Annual Meeting Chair

Jennifer Rosenberg

Director, Meetings and Events

Jennifer Rosenberg, CMP
Director, Meetings and Events
1313 Dolley Madison Blvd.
Suite 402
McLean VA 22101
703-790-1745 **Ex. 6**
Fax: 703-790-2672
jrosenberg@burkinc.com

Message

**From:** Roy Bailey [rbailey@gdcillc.com]
**Sent:** 7/16/2017 6:19:20 PM
**To:** Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
**CC:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** Re: Memo

Thanks very much. Enjoy your afternoon.

Best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

On Jul 16, 2017, at 10:42 AM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:

> Thanks! I'll bring her up to speed on our recent conversation. Will report back this week.
>
> Sent from my iPhone
>
> On Jul 16, 2017, at 1:41 PM, Roy Bailey <rbailey@gdcillc.com> wrote:
>
> > Yes, we know Nancy is the expert in this area.
> >
> > Our friends at Intrexon would be happy to jump on a call anytime to give their insight and input if helpful.
> >
> > Best regards
> >
> > Roy W. Bailey
> > CEO
> > Giuliani Deason Capital Interests, LLC
> > Cell Ex. 6
> > Office Ex. 6
> > Rbailey@gdcillc.com
> > Rbailey@baileystrategicadvisors.com
> >
> > On Jul 16, 2017, at 10:35 AM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:
> >
> > > Thank you! Nancy is our expert here and I'll huddle with her on this.

On Jul 16, 2017, at 1:34 PM, Roy Bailey <rbailey@gdcillc.com> wrote:

> Thanks so much for the call. I have attached the memo which should outline the concerns.
>
> Intrexon ( OXITEC ) execs are pleased to jump on a call anytime to discuss.
>
> Thanks so much

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

> **From:** "Bobo, Jack" <JBobo@intrexon.com>
> **Date:** July 15, 2017 at 6:59:38 PM PDT
> **To:** 'Roy Bailey' <rbailey@gdcillc.com>
> **Subject: Memo**
>
> ---
>
> 

documents from your system immediately, without copying, reviewing or otherwise using them for any purpose. Thank you for your cooperation.

<EPA Improperly Granted the Wolbachia EUP.DOCX>

Message

**From**: Roy Bailey [rbailey@gdcillc.com]
**Sent**: 7/16/2017 5:38:48 PM
**To**: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**CC**: Roy Bailey [rbailey@gdcillc.com]; Gay Ludwick [gay@gdcillc.com]
**Subject**: Fwd: Wolbachia doc
**Attachments**: Wolbachia Overview and Publications Citing Concerns and Risks.docx; ATT00001.htm

**Flag**: Flag for follow up

Tate,

This additional info may be helpful as well. Thanks so much for your call and attention to the concerns.

Best regards

Roy W. Bailey
CEO
Giuliani Deason Capital Interests, LLC
Cell Ex. 6
Office Ex. 6
Rbailey@gdcillc.com
Rbailey@baileystrategicadvisors.com

Begin forwarded message:

> **From:** "Basta, Christopher" <CBasta@intrexon.com>
> **Date:** July 16, 2017 at 10:22:45 AM PDT
> **To:** Roy Bailey <rbailey@gdcillc.com>
> **Cc:** "Kirk, Randal J" <RJ.Kirk@intrexon.com>, "Bobo, Jack" <JBobo@intrexon.com>
> **Subject: Wolbachia doc**
>
> Roy,
>
> RJ asked that I send you this document that provides a Wolbachia overview as well as a list of publications that cover various Wolbachia concerns & potential issues.
>
> Best,
> Chris
>
> **Christopher Basta**
> Vice President, Investor Relations
> **Intrexon Corporation**
> Work Ex. 6

Cell: Ex. 6
www.dna.com

**OVERVIEW OF WOLBACHIA CONCERNS**

Serious and very basic questions remain as to the potential adverse threats that *Wolbachia* poses to human health and the environment.

*Wolbachia*, a complex bacterium known to biologically alter its hosts, is found in many different insects in nature. Yet that does not make its artificial insertion into *Aedes aegypti* as a population control method "natural" or "safe". In fact in cases where *Wolbachia* inhabits insects that bite humans such as mosquitoes and flies, negative effects have been documented in several peer-reviewed publications. Therefore using *Wolbachia* as a mosquito control solution may present a significant biosafety risk.

Notably, if Wolbachia infected males and females mate it leads to viable offspring and that would result in Wolbachia-infected mosquitoes perpetually persisting in the environment. If something goes wrong there will be no recall.

Here are some currently known risks found in human-biting flies and mosquitoes infected with *Wolbachia* include:

- *Wolbachia* holds several key roles in River Blindness which begins with a bite of a blackfly. River Blindness infects up to 25 million people globally and is the second most common infectious cause of blindness;
- *Wolbachia* has been attributed to major lymphatic inflammation associated with Elephantiasis, also known as lymphatic filariasis, which is spread by the bites of infected mosquitoes;
- *Wolbachia* significantly enhances West Nile virus infection in mosquitoes increasing risk of transmission to humans;
- *Wolbachia* enhances malaria parasite infection in mosquitoes increasing risk of transmission to humans; and
- *Wolbachia* has been naturally found in certain mosquitoes (not artificially inserted in a lab), and those infected mosquitoes still are able to transmit dangerous viruses such as dengue and chikungunya.

In addition to these direct and dangerous threats to humans, another concern seems to be overlooked by many. *Wolbachia* transfers genes to its hosts through a process called Horizontal Gene Transfer. This means this insect control method using *Wolbachia* can effectively introduce over 1,000 new genes into its mosquito hosts (as compared to recombinant genetic engineering which typically introduces a few genes or less). This random genetic engineering is not well-defined or understood, yet it is evident that every time *Wolbachia* invades a host the result is a "GMO".

- Peer review papers show that *Wolbachia* genetically engineers its hosts as it transfers its DNA into insect genomes and these genes are expressed. In the *Aedes aegypti* mosquito there are genes that share high homology to *Wolbachi*a suggesting that gene transfer has happened over an evolutionary time scale and that these genes have functional significance; and
- Newly published evidence confirms that *Wolbachia* has a virus that encodes and causes the expression of a toxin from the Black widow spider that is hypothesized to form pores in cell membranes. If mosquitoes that carry *Wolbachia* with this virus are released, the effects of this virus are unknown as are the consequences of these mosquitoes biting people.

The following pages have a list the publications that have cited various concerns/issues/risks with Wolbachia.

**PUBLICATIONS AND AUTHORS CITING CONCERNS/RISKS AROUND *WOLBACHIA*:**

- **Publications 1 – 11:** Cover pathogen increase, horizontal gene transfer, lack of effect in varying climate environments
- **Publication 12**: Covers revelation regarding black-widow spider venom gene ending up in a virus that infects Wolbachia
- **Publications 13 - 15:** Cover Wolbachia's role in River Blindness & Lymphatic Filariasis

1. Wolbachia Can Enhance Plasmodium Infection in Mosquitoes: Implications for Malaria Control?
   http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004182
   - Excerpt - ***Any potential control strategy devised in regions where more than one parasite species occurs needs to thoroughly investigate the effect of Wolbachia on all parasite species transmitted by the vector, as well as other pathogens such as filarial worms or arboviruses to ensure that Wolbachia-infected mosquitoes do not inadvertently enhance transmission of secondary pathogens.***
   - Authors - Grant L. Hughes, Ana Rivero, Jason L. Rasgon

2. Wolbachia Enhances West Nile Virus (WNV) Infection in the Mosquito Culex tarsalis
   http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965
   - Excerpt – ***This is the first observation of* Wolbachia*-induced enhancement of a human pathogen in mosquitoes, suggesting that caution should be applied before releasing Wolbachia-infected insects as part of a vector-borne disease control program.***
   - Authors - Brittany L. Dodson, Grant L. Hughes, Oluwatobi Paul, Amy C. Matacchiero, Laura D. Kramer, Jason L. Rasgon

3. Wolbachia increases susceptibility to Plasmodium infection in a natural system
   http://rspb.royalsocietypublishing.org/content/281/1779/20132837
   - Excerpt - ***These results suggest that naturally Wolbachia-infected mosquitoes may, in fact, be better vectors of malaria than Wolbachia-free ones.***
   - Authors - F. Zélé, A. Nicot, A. Berthomieu, M. Weill, O. Duron, A. Rivero

4. Wolbachia Strain wAlbB Enhances Infection by the Rodent Malaria Parasite Plasmodium berghei in Anopheles gambiae Mosquitoes
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294472/
   - Excerpt - ***Wolbachia, a common bacterial endosymbiont of insects, has been shown to protect its hosts against a wide range of pathogens. However, not all strains exert a protective effect on their host. We show that the wAlbB strain significantly increases P. berghei oocyst levels in the mosquito midgut while wMelPop modestly suppresses oocyst levels. The wAlbB strain is avirulent to mosquitoes while wMelPop is moderately virulent to mosquitoes pre-blood meal and highly virulent after mosquitoes have fed on mice.***

***These various effects on P. berghei levels suggest that Wolbachia strains differ in their interactions with the host and/or pathogen…***

- Authors - Grant L. Hughes, Joel Vega-Rodriguez, Ping Xue, and Jason L. Rasgon

5. Wolbachia in a major African crop pest increases susceptibility to viral disease rather than protects.
   https://www.ncbi.nlm.nih.gov/pubmed/22731846
   - Excerpt – ***Wolbachia have generated considerable recent interest due to the capacity of some strains to protect their insect hosts against viruses and the potential for this to reduce vector competence of a range of human diseases, including dengue. In contrast, here we provide data from field populations of a major crop pest, African armyworm (Spodoptera exempta), which show that the prevalence and intensity of infection with a nucleopolydrovirus (SpexNPV) is positively associated with infection with three strains of Wolbachia***
   - Authors - Graham RI, Grzywacz D, Mushobozi WL, Wilson K.

6. Temperature alters Plasmodium blocking by Wolbachia.
   https://www.ncbi.nlm.nih.gov/pubmed/24488176
   - Excerpt – ***Very recently, the Asian malaria vector (Anopheles stephensi) was stably transinfected with the wAlbB strain of Wolbachia, inducing refractoriness to the human malaria parasite Plasmodium falciparum. However, conditions in the field can differ substantially from those in the laboratory. Our results demonstrate complex effects of temperature on the Wolbachia-malaria interaction, and suggest the impacts of transinfection might vary across diverse environments.***
   - Authors - Murdock CC, Blanford S, Hughes GL, Rasgon JL, Thomas MB.

7. Horizontal gene transfer between Wolbachia and the mosquito Aedes aegypti.
   https://www.ncbi.nlm.nih.gov/pubmed/19154594
   - Excerpt – ***The evolutionary importance of horizontal gene transfer (HGT) from Wolbachia endosymbiotic bacteria to their eukaryotic hosts is a topic of considerable interest and debate…We have discovered a case of HGT, involving two adjacent genes, between the genomes of Wolbachia and the currently Wolbachia-uninfected mosquito Aedes aegypti, an important human disease vector…The data support the argument that HGT between Wolbachia endosymbiotic bacteria and their hosts has produced evolutionary innovation.***
   - Authors - Klasson L, Kambris Z, Cook PE, Walker T, Sinkins SP

8. A case of horizontal gene transfer from Wolbachia to Aedes albopictus C6/36 cell line
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013104/
   - Excerpt - ***Horizontal gene transfer plays an essential role in evolution and ecological adaptation, yet this phenomenon has remained controversial, particularly where it occurs between prokaryotes and eukaryotes. In this study, we report the discovery of a horizontal gene transfer from the endosymbiont Wolbachia in the C6/36 cell line derived from the***

***mosquito Aedes albopictus. Moreover, we report that this horizontally transferred gene displayed high transcription level. This finding and the results of further experimentation strongly suggest this gene is functional and has been expressed and translated into a protein in the mosquito host cells.***

- Authors - Qing Hou , Ji He, Jing Yu, Yuting Ye, Dan Zhou, Yan Sun, Donghui Zhang, Lei Ma, Bo Shen, and Changliang Zhu

9. Widespread lateral gene transfer from intracellular bacteria to multicellular eukaryotes. https://www.ncbi.nlm.nih.gov/pubmed/17761848
   - Excerpt – ***Although common among bacteria, lateral gene transfer-the movement of genes between distantly related organisms-is thought to occur only rarely between bacteria and multicellular eukaryotes. However, the presence of endosymbionts, such as Wolbachia pipientis, within some eukaryotic germlines may facilitate bacterial gene transfers to eukaryotic host genomes. We found and confirmed transfers into the genomes of four insect and four nematode species that range from nearly the entire Wolbachia genome (>1 megabase) to short (<500 base pairs) insertions.***
   - Authors - Dunning Hotopp JC, Clark ME, Oliveira DC, Foster JM, Fischer P, Muñoz Torres MC, Giebel JD, Kumar N, Ishmael N, Wang S, Ingram J, Nene RV, Shepard J, Tomkins J, Richards S, Spiro DJ, Ghedin E, Slatko BE, Tettelin H, Werren JH.

10. Genome fragment of Wolbachia endosymbiont transferred to X chromosome of host insect http://www.pnas.org/content/99/22/14280.full
    - Excerpt – ***Here we report an unprecedented case of prokaryote–eukaryote horizontal gene transfer: a genome fragment from the Wolbachia endosymbiont has been transferred to the X chromosome of a beetle.....The adzuki bean beetle, Callosobruchus chinensis, is triple-infected with distinct lineages of Wolbachia endosymbiont, wBruCon, wBruOri, and wBruAus, which were identified by their wsp (Wolbachia surface protein) gene sequences. Whereas wBruCon and wBruOri caused cytoplasmic incompatibility of the host insect, wBruAus did not. Although wBruCon and wBruOri were easily eliminated by antibiotic treatments, wBruAus persisted over five treated generations and could not be eliminated...The study's results strongly suggest that wBruAus has no microbial entity but is a genome fragment of Wolbachia endosymbiont transferred to the X chromosome of the host insect.***
    - Authors - Natsuko Kondo, Naruo Nikoh, Nobuyuki Ijichi, Masakazu Shimada, and Takema Fukatsu

11. Phylogenetic relationships of the Wolbachia of nematodes and arthropods. https://www.ncbi.nlm.nih.gov/pubmed/17040125
    - Excerpt - ***Using the wOvo sequence, we identified a lateral transfer event whereby segments of the Wolbachia genome were inserted into the Onchocerca nuclear genome. This event predated the separation of the human parasite O. volvulus from its cattle-parasitic sister species, O. ochengi. The long association between filarial nematodes and***

***Wolbachia symbionts may permit more frequent genetic exchange between their genomes.***

- Authors - Fenn K, Conlon C, Jones M, Quail MA, Holroyd NE, Parkhill J, Blaxter M

12. Eukaryotic association module in phage WO genomes from Wolbachia
http://www.nature.com/articles/ncomms13155
    - Excerpt - ***Here we report a metagenomic analysis of purified bacteriophage WO particles of Wolbachia and uncover a eukaryotic association module in the complete WO genome. It harbours predicted domains, such as the black widow latrotoxin C-terminal domain, that are uninterrupted in bacteriophage genomes, enriched with eukaryotic protease cleavage sites and combined with additional domains to forge one of the largest bacteriophage genes to date (14,256 bp). To the best of our knowledge, these eukaryotic-like domains have never before been reported in packaged bacteriophages and their phylogeny, distribution and sequence diversity imply lateral transfers between bacteriophage/prophage and animal genomes. Finally, the WO genome sequences and identification of attachment sites will potentially advance genetic manipulation of Wolbachia.***
    - Authors - Sarah R. Bordenstein & Seth R. Bordenstein

13. Onchocerciasis: the Role of Wolbachia Bacterial Endosymbionts in Parasite Biology, Disease Pathogenesis, and Treatment
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131055/
    - Excerpt - ***Studies with other filarial nematode species have also highlighted a role for Wolbachia in transmission and infection of the mammalian host through a fascinating manipulation of mast cell-mediated vasodilation to enhance infectivity of vector-borne larvae. Wolbachia has also been identified as the principal driver of innate and adaptive Th1 inflammatory immunity, which can either contribute to disease pathogenesis or, with the Wolbachia-mediated recruitment of mast cells, enhance infectivity. The Wolbachia activation of innate inflammation also drives inflammatory adverse events in response to chemotherapy with either diethylcarbamazine (DEC) or ivermectin. In this review we summarize the experimental and field trial data which have uncovered the importance of Wolbachia symbiosis in onchocerciasis.***
    - Authors –

14. The Role of Endosymbiotic Wolbachia Bacteria in the Pathogenesis of River Blindness
http://www.nature.com/news/2002/020304/full/news020304-9.html
    - Excerpt – ***Using a murine model for river blindness in which soluble extracts of filarial nematodes were injected into the corneal stroma, we demonstrated that the predominant inflammatory response in the cornea was due to species to endosymbiotic Wolbachia bacteria. In addition, the inflammatory response induced by these bacteria was dependent on expression of functional Toll-like receptor (TLR4) on host cells.***

- Authors - Amélie v. Saint André, Nathan M. Blackwell, Laurie R. Hall, Achim Hoerauf, Norbert W. Brattig, Lars Volkmann, Mark J. Taylor, Louise Ford, Amy G. Hise, Jonathan H. Lass, Eugenia Diaconu, Eric Pearlman

15. Wolbachia bacteria in filarial immunity and disease.
https://www.ncbi.nlm.nih.gov/pubmed/11472559
    - Excerpt - ***Lymphatic filarial nematodes are infected with endosymbiotic Wolbachia bacteria. Lipopolysaccharide from these bacteria is the major activator of innate inflammatory responses induced directly by the parasite. Here, we propose a mechanism by which Wolbachia initiates acute inflammatory responses associated with death of parasites, leading to acute filarial lymphangitis and adverse reactions to antifilarial chemotherapy. We also speculate that repeated exposure to acute inflammatory responses and the chronic release of bacteria, results in damage to infected lymphatics and desensitization of the innate immune system. These events will result in an increased susceptibility to opportunistic infections, which cause acute dermatolymphangitis associated with lymphoedema and elephantiasis***
    - Authors - Taylor MJ, Cross HF, Ford L, Makunde WH, Prasad GB, Bilo K.

Message

**From:** White, Kimberly [Kimberly_White@americanchemistry.com]
**Sent:** 5/22/2017 11:32:02 AM
**To:** Goldstein, Bernard D [bdgold@pitt.edu]
**CC:** Rick_Becker@americanchemistry.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f03aaee7f1014aad916f86c53f886717-Rick_Becker@americanchemistry.com]; Joe Arvai [jlarvai@umich.edu]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** RE: Follow-up on SRA Session

Dear Bernie:

I'm okay with your changes. Thanks

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: Ex. 6 C: Ex. 6
www.americanchemistry.com

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Monday, May 22, 2017 5:24 AM
**To:** White, Kimberly
**Cc:** Becker, Rick; Joe Arvai; Beck, Nancy
**Subject:** RE: Follow-up on SRA Session

Hi Kimberly

Your changes are OK with me, but I have added a few words ("and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes") to reflect the substantial concern of the academic community about the following provision in the SAB Act. (I also think that the provision is short-sighted from an industry perspective).

"(H) a Board member shall have no current grants or contracts from the Environmental Protection Agency
and shall not apply for a grant or contract for 3 years following the end of that member's service on the Board."

There is also other language in the Act which could be interpreted as the above provision being applicable to not only full SAB Board membership, but to the members of any EPA review process of any hazard or risk assessment

Let me know if the new language is acceptable to you. I'm also copying Joe Arvai and Nancy Beck in case they want to respond, either in writing or by phone, particularly as there is now no description of Administrator Pruitt's goals or activities in this area. While not necessary, we do have room in the abstract for additional language

Bernie

Bernard D. Goldstein, MD
Professor Emeritus and Dean Emeritus
University of Pittsburgh Graduate School of Public Health
130 Desoto St; Rm A-710
Pittsburgh PA 15261
Office: 412 648 9994
Cell: Ex. 6

---

**From:** White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
**Sent:** Friday, May 19, 2017 6:22 PM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Cc:** Becker, Rick <Rick_Becker@americanchemistry.com>
**Subject:** RE: Follow-up on SRA Session

Dear Bernie:

Thanks for the additional information about the session and the abstract. We offer some suggestions to the abstract attached. The suggestions attempt to focus the abstract on the discussion regarding what are appropriate approaches for optimal provision of scientific advice to regulatory agencies and work to adjust some of the language that may be perceived as inflammatory.

Kind Regards,

Kimberly

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: Ex. 6 C: Ex. 6
www.americanchemistry.com

---

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Friday, May 19, 2017 2:53 PM
**To:** White, Kimberly
**Cc:** Becker, Rick
**Subject:** RE: Follow-up on SRA Session

Dear Dr White

Great news!!

My previous email to you is below; along with the original attachment of the preliminary draft

Bernie

---

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh

Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994

---

Dear Dr White

I am following up with you at the suggestion of Nancy Beck (email below) to request your involvement in a proposal for a Roundtable to be submitted to the Society for Risk Analysis for its annual meeting in Crystal City next December 10-13. I've attached a short overview of Roundtables from the SRA web site along with a rough draft of the abstract. I am trying to focus the Roundtable on the parameters governing an effective science advisory process for a regulatory agency, rather than on the current controversy – although this is unlikely to be fully possible.

NOTE: no abstract would be needed from you, just an agreement to participate, give perhaps a 10 minute presentation and participate in the discussion during the 90 minute session. But your input on the proposal would be welcome.

One difference from the note below to Nancy is that I have been told that the proposal is more likely to be acceptable if it has a broader range of participants so it will probably 4-5 speakers rather than 3-4.

I had previously reached out to Richard Becker asking for whom to approach at ACC now that Nancy had left. His response was that ACC would be interested in participating but only if EPA did as well, which I fully understand. I know he is out of town today. As you no doubt know, ACC is on record supporting the EPA SAB Act that passed the House.

There are some time constraints in getting this completed, particularly as I will be at Dow Chemical for much of next week, so hope both that you can do this and that you can respond by midweek

Many thanks for your consideration

Bernie

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh
Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994

**From:** Goldstein, Bernard D
**Sent:** Thursday, May 18, 2017 2:28 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** Re: SRA panel

Happy to reframe. I originally had a quote from the congressman who sponsored it but this seemed too inflammatory for SRA. Will look at this again tonight and will contact Kimberly White

Sent from my iPhone

On May 18, 2017, at 12:08 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

Bernie,
I think the framing of the abstract is a bit biased and needs some work.
I cant and wont speak for ACC at all, but for this topic, I direct you to Kimberly White. She has testified in front of congress on these issues. Kimberly_White@americanchemistry.com.

If I have more time this week I will noodle the abstract but it's a bit of a busy time here.

Regards,
Nancy

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Wednesday, May 17, 2017 12:41 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** RE: SRA panel

Hi Nancy

Great to hear!!

Attached is what I've written so far, and some of the directions from the SRA web site. I'm about to run out for most of the rest of the afternoon. I'd like to get this out of the way as soon as reasonably possible as am at meetings at Dow most of next week.

No abstract would be needed from you so there is nothing written with your name on it that would have to go through the EPA process, at least as I understood it many, many years ago. (As the proposer, I would be the only one with my name on the proposed abstract, but would welcome your input and that of the other panelists on the proposal).

I'm envisioning the 3 or 4 panelists for the Roundtable would have about 15 min each for presentation and the rest of the 90 minutes would be for a facilitated discussion led by the moderator

I'm thinking of asking Granger Morgan or Terry Yosie to be the moderator, but your suggestion for moderator or for another panelist who supports the ACC position on the SAB Act would be very much appreciated.

Best regards

Bernie

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh

Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994
Cell Ex. 6

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Wednesday, May 17, 2017 12:22 PM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Subject:** SRA panel

Hi Bernie,
Got your message and am happy to consider the request. Can you send me all the information on the proposal (abstract, goals, participants, etc)?
I will have to find out if I have to run this through a clearance process—not sure how that works yet and if those procedures apply to me.
Thanks,
Nancy

**********

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
**Sent:** Friday, May 19, 2017 2:35 PM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Cc:** Becker, Rick <Rick_Becker@americanchemistry.com>
**Subject:** Follow-up on SRA Session

Dear Dr. Goldstein:

Thank you for your voicemail earlier today. I have had an opportunity to follow-up with Rick (cc'd on this email) and I understand you have a commitment from EPA to participate. Given the confirmation of EPA's participation, we will also confirm ACC's participation. Could you send me the proposed abstract or session description? Also it would be helpful to know of any additional information you need from ACC for the session and any deadlines.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: Ex. 6 C: Ex. 6
www.americanchemistry.com

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Message

**From:** Goldstein, Bernard D [bdgold@pitt.edu]
**Sent:** 5/22/2017 9:23:56 AM
**To:** White, Kimberly [Kimberly_White@americanchemistry.com]
**CC:** Rick_Becker@americanchemistry.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f03aaee7f1014aad916f86c53f886717-Rick_Becker@americanchemistry.com]; Joe Arvai [jlarvai@umich.edu]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
**Subject:** RE: Follow-up on SRA Session
**Attachments:** SRA ROUNDTABLE+Suggested Edits plus BDG.docx

**Flag:** Flag for follow up

Hi Kimberly

Your changes are OK with me, but I have added a few words ("and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes") to reflect the substantial concern of the academic community about the following provision in the SAB Act. (I also think that the provision is short-sighted from an industry perspective).

"(H) a Board member shall have no current grants or contracts from the Environmental Protection Agency
and shall not apply for a grant or contract for 3 years following the end of that member's service on the Board."

There is also other language in the Act which could be interpreted as the above provision being applicable to not only full SAB Board membership, but to the members of any EPA review process of any hazard or risk assessment

Let me know if the new language is acceptable to you. I'm also copying Joe Arvai and Nancy Beck in case they want to respond, either in writing or by phone, particularly as there is now no description of Administrator Pruitt's goals or activities in this area. While not necessary, we do have room in the abstract for additional language

Bernie

Bernard D. Goldstein, MD
Professor Emeritus and Dean Emeritus
University of Pittsburgh Graduate School of Public Health
130 Desoto St; Rm A-710
Pittsburgh PA 15261
Office: 412 648 9994
Cell: **Ex. 6**

**From:** White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
**Sent:** Friday, May 19, 2017 6:22 PM

**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Cc:** Becker, Rick <Rick_Becker@americanchemistry.com>
**Subject:** RE: Follow-up on SRA Session

Dear Bernie:

Thanks for the additional information about the session and the abstract. We offer some suggestions to the abstract attached. The suggestions attempt to focus the abstract on the discussion regarding what are appropriate approaches for optimal provision of scientific advice to regulatory agencies and work to adjust some of the language that may be perceived as inflammatory.

Kind Regards,

Kimberly

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
O: Ex. 6 C: Ex. 6
www.americanchemistry.com

---

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Friday, May 19, 2017 2:53 PM
**To:** White, Kimberly
**Cc:** Becker, Rick
**Subject:** RE: Follow-up on SRA Session

Dear Dr White

Great news!!

My previous email to you is below; along with the original attachment of the preliminary draft

Bernie

---

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh
Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994

---

Dear Dr White

I am following up with you at the suggestion of Nancy Beck (email below) to request your involvement in a proposal for a Roundtable to be submitted to the Society for Risk Analysis for its annual meeting in Crystal City next December 10-13. I've attached a short overview of Roundtables from the SRA web site along with a rough draft of the abstract. I am trying to focus the Roundtable on the parameters governing an effective science advisory process for a regulatory agency, rather than on the current controversy – although this is unlikely to be fully possible.

NOTE: no abstract would be needed from you, just an agreement to participate, give perhaps a 10 minute presentation and participate in the discussion during the 90 minute session. But your input on the proposal would be welcome.

One difference from the note below to Nancy is that I have been told that the proposal is more likely to be acceptable if it has a broader range of participants so it will probably 4-5 speakers rather than 3-4.

I had previously reached out to Richard Becker asking for whom to approach at ACC now that Nancy had left. His response was that ACC would be interested in participating but only if EPA did as well, which I fully understand. I know he is out of town today. As you no doubt know, ACC is on record supporting the EPA SAB Act that passed the House.

There are some time constraints in getting this completed, particularly as I will be at Dow Chemical for much of next week, so hope both that you can do this and that you can respond by midweek

Many thanks for your consideration

Bernie

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh
Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994

**From:** Goldstein, Bernard D
**Sent:** Thursday, May 18, 2017 2:28 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** Re: SRA panel

Happy to reframe. I originally had a quote from the congressman who sponsored it but this seemed too inflammatory for SRA. Will look at this again tonight and will contact Kimberly White

Sent from my iPhone

On May 18, 2017, at 12:08 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

Bernie,
I think the framing of the abstract is a bit biased and needs some work.
I cant and wont speak for ACC at all, but for this topic, I direct you to Kimberly White. She has testified in front of congress on these issues. Kimberly_White@americanchemistry.com.

If I have more time this week I will noodle the abstract but it's a bit of a busy time here.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Goldstein, Bernard D [mailto:bdgold@pitt.edu]
**Sent:** Wednesday, May 17, 2017 12:41 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** RE: SRA panel

Hi Nancy

Great to hear!!

Attached is what I've written so far, and some of the directions from the SRA web site. I'm about to run out for most of the rest of the afternoon. I'd like to get this out of the way as soon as reasonably possible as am at meetings at Dow most of next week.

No abstract would be needed from you so there is nothing written with your name on it that would have to go through the EPA process, at least as I understood it many, many years ago. (As the proposer, I would be the only one with my name on the proposed abstract, but would welcome your input and that of the other panelists on the proposal).

I'm envisioning the 3 or 4 panelists for the Roundtable would have about 15 min each for presentation and the rest of the 90 minutes would be for a facilitated discussion led by the moderator

I'm thinking of asking Granger Morgan or Terry Yosie to be the moderator, but your suggestion for moderator or for another panelist who supports the ACC position on the SAB Act would be very much appreciated.

Best regards

Bernie

Bernard D. Goldstein, MD
Emeritus Professor and Emeritus Dean
Graduate School of Public Health
University of Pittsburgh
Rm A710 Crabtree Hall
130 De Soto St
Pittsburgh, PA 15261
Phone 412 648 9994
Cell Ex. 6

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Wednesday, May 17, 2017 12:22 PM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Subject:** SRA panel

Hi Bernie,
Got your message and am happy to consider the request. Can you send me all the information on the proposal (abstract, goals, participants, etc)?

I will have to find out if I have to run this through a clearance process—not sure how that works yet and if those procedures apply to me.
Thanks,
Nancy

**********

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M Ex. 6
beck.nancy@epa.gov

**From:** White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
**Sent:** Friday, May 19, 2017 2:35 PM
**To:** Goldstein, Bernard D <bdgold@pitt.edu>
**Cc:** Becker, Rick <Rick_Becker@americanchemistry.com>
**Subject:** Follow-up on SRA Session

Dear Dr. Goldstein:

Thank you for your voicemail earlier today. I have had an opportunity to follow-up with Rick (cc'd on this email) and I understand you have a commitment from EPA to participate. Given the confirmation of EPA's participation, we will also confirm ACC's participation. Could you send me the proposed abstract or session description? Also it would be helpful to know of any additional information you need from ACC for the session and any deadlines.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
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**Preliminary Draft Proposal for SRA Platform Topic**
**December 2017, Arlington Va**

## SRA ROUNDTABLE RULES (Deadline May 31)

"A roundtable addresses a high-visibility topic of special interest in a 90-minute panel discussion format.
Only a small number can be considered per space and schedule constraints. The organizer submits an abstract that describes the topic and what the audience should expect to gain from the discussion; the organizer also lists the moderator, panelists, and their emails."

Draft Title: What is the Optimal Approach to Organizing Governmental Risk-Related Science Advisory Processes

Draft Abstract (maximum is 2,000 characters - approx. 300 words)

Recent ~~controversial~~ activities by both Congress and by EPA Administrator Pruitt provide an opportunity to evaluate approaches for ~~rethink the appropriate approach to~~ organizing risk-related scientific advisory processes for regulatory agencies. The EPA Science Advisory Board Reform Act~~(title of bill)~~ has been passed by the US House of Representatives and is awaiting action in the US Senate, which may or may or may not be forthcoming. ~~(briefly describe Act and announced EPA actions).~~ These have generated media interest and controversy and some have characterized these actions as unnecessarily politicizing science and decreasing the likelihood of the involvement of knowledgeable academic scientists in EPA review processes. Others have pointed out that there's a need to ~~The rationale for these implementing changes in the advisor panels related to~~ broaden~~ing~~ scientific representation in diverse fields, and to improve procedures for balanc-ing perspectives and perceived biases on EPA scientific advisory panels. ~~changes is the perception that EPA advisory processes for selection of scientists and for interaction of the scientists with EPA staff have inappropriately skewed the interpretation of the science underlying risk-related regulations in favor of overly aggressive actions inimical to the US economy. On the other hand, the congressional Act and Administrator Pruitt's actions have been criticized for being overly friendly to industry interests and for politicizing the scientific advisory process. While the current controversy will not be totally avoided, t~~The Roundtable participants will be asked to focus on the underlying principles that should guide the science advisory processes for the optimal provision of scientific advice on risk-related issues to a regulatory agency.

Message

**From:** Dourson, Michael (doursoml) [doursoml@ucmail.uc.edu]
**Sent:** 6/5/2017 10:08:41 PM
**To:** Akihiko Hirose [akihikoh@dranihs.net]; Ex. 6 'Michael L. Caldwell' [MCaldwell@zacfirm.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Birchfield, Norman [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c910f2fd28414e819b6afe6dda525e9f-Birchfield, Norman]; yamazaki [k-yamazaki@jisha.or.jp]; kmdilwali@intsci.com; 'Michael L. Caldwell' [MCaldwell@zacfirm.com]; Pierre_Therriault@hc-sc.gc.ca; Richard Charron [Richard.Charron@hc-sc.gc.ca]; Sams, Reeder [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7d5b479ccd894cea99ae55df20de6971-Sams, Reeder]; mhoneycu@tceq.state.tx.us [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d08fcaf8d2c44901954b8b8d40c968a3-mhoneycu@tceq.state.tx.us]; Deshpande, Satish (MOECC) [Satish.Deshpande@ontario.ca]; sarah.labib@canada.ca [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=497a7a27414f4b168439b6b95cc8ec65-sarah.labib]; Shannon Ethridge [sethridg@tceq.state.tx.us]; Barbara Sassi [barbara.sassi@health.mo.gov]; dennis.wambuguh@health.mo.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9288a38c575842fa9b9e75e1a325cb3c-dennis.wambuguh@health.mo.gov]; Chris Prucha [cprucha@wm.com]; h-kano@jisha.or.jp; Maier, Michael (maierma) [maierma@ucmail.uc.edu]; t-kasai@jisha.or.jp; sethridg@tceq.state.tx.us; Robert Maronpot Ex. 6 Whalan, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fb12b5d4bd5e4bd88ccde4f514c56a8e-Whalan, John]; James E. Klaunig [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=95573202fd414b80b0699a2f050205b4-James E. Kl]; Jayne Wright [jayne@jaynewright.co.uk]; Nadine Weinberg [nadine.weinberg@erm.com]; Garoutte, Jonathan [Jonathan.Garoutte@health.mo.gov]; flagac@michigan.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=14932891d913461e9c46e752b77806e5-flagac@michigan.gov]; Joseph.Haney@tceq.texas.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e61ef49e06df4a1f9675eec8b0177c1e-Joseph.Haney@tceq.texas.gov]; Phelka, Amanda [aphelka@nsf.org]; jenglish@nsf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fd86cc8b2131406993360dd89af0464f-jenglish@nsf.org]; Laessig, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d2bff1b8898f425e8001b9beca03014a-Laessig, Susan]; Herbert, Ron (NIH/NIEHS) [E] [herbert@niehs.nih.gov]; oono-yurie@mhlw.go.jp; toxpathmcc [toxpathmcc@bellsouth.net]; Jeff.Wenzel@health.mo.gov; Maria Hegstad [mhegstad@iwpnews.com]; Doug Wolf [Wolf.Doug@epamail.epa.gov]; helen.goeden@state.mn.us [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b567d1e3f235405783e08b0064579be0-helen.goeden@state.mn.us]; James.kelly@state.mn.us [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f42c95c6e0cb484dab59140f6136fa84-James.kelly@state.mn.us]; Franz, Christina [Christina_Franz@americanchemistry.com]; Kylie Brockenfelt [KBrockenfelt@epl-inc.com]; riesd@michigan.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a989ecdcc6514a5fb11354a2f94aa001-riesd@michigan.gov]; 'Sager, Shawn' [Shawn.Sager@arcadis.com]; HOWARD, WILLIAM B GS-13 USAF AFMC AFCEC/CZTE [william.howard.40@us.af.mil]; Hamlin, Mel (NIH/NIEHS) [C] (hamlin@niehs.nih.gov) [hamlin@niehs.nih.gov]; ruckner@rx.uga.edu; Harvey Clewell [HClewell@thehamner.org]; david_dorman@ncsu.edu; fjmiller@nc.rr.com; rpsharma@uga.edu; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]
**CC:** Jeri.Higginbotham@ky.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3df2f5c8787c4041b7da55f03478c30c-Jeri.Higginbotham@ky.gov]; jcrum@hampmathews.com; burleighflayer@ppg.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e4176125deb042129502188461413347-burleighflayer@ppg.com]; Nance, Patricia (nancepm) [nancepm@ucmail.uc.edu]; 'Forsberg, Norman' [Norman.Forsberg@arcadis.com]; 'Mark Lafranconi' [Mark.Lafranconi@erm.com]; Reichard, John (reichajf) [reichajf@ucmail.uc.edu]
**Subject:** In Print---1,4-Dioxane Publication
**Attachments:** E1E8A4B9-00D9-4B4E-B4FF-FD948FB9EF92[2].jpg; 914B179D-BFBE-428C-AB4C-901DB9340CC1[2].png

Dear Colleagues

On behalf of the authors, I am pleased to let you know that our publication is now in print as shown below. The paper was developed under the umbrella of the Alliance for Risk Assessment (*ARA*), and is open access thanks to Norm Forsberg and his company Arcadis. Please feel free to share this paper as needed.

Cheers!

Michael Dourson

*— Risk Science Center (formerly TERA Center) sponsors the International Toxicity Estimates for Risk (ITER) database of risk assessment values on Toxnet: http://toxnet.nlm.nih.gov/*


**From:** RSS Feed via IFTTT <weeklydigest@ifttt.com>
**Date:** Monday, June 5, 2017 at 8:14 AM
**To:** Michael Dourson <doursoml@ucmail.uc.edu>
**Subject:** Weekly Digest: If new feed item from http://rss.sciencedirect.com/publication/science/02732300, then add to weekly digest sent to michael.dourson@uc.edu on (7 items)

## Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1

Publication date: August 2017
**Source:**Regulatory Toxicology and Pharmacology, Volume 88
Author(s): Michael L. Dourson, Jeri Higginbotham, Jeff Crum, Heather Burleigh-Flayer, Patricia Nance, Nor
Previous work has shown that the weight of evidence supports the hypothesis that 1,4-dioxane causes liv
been resolved, however. In the current work, a reanalysis of data from two chronic mouse cancer bioassa
the appearance of liver tumors with a high background incidence, support the conclusion that rodent live
higher doses of the parent compound cause an ever increasing toxicity in the rodent liver as evidenced by
can be excluded. The observed liver toxicity has a threshold in the dose scale at or below levels that satur
toxicity are supported by the non-mutagenic, metabolic saturation kinetics, and cytotoxicity-generated re

via ScienceDirect Publication: Regulatory Toxicology and Pharmacology http://ift.tt/2r6ix2E May 30, 2017

via RSS
Feed http://rss.sciencedirect.com/action/redirectFile?&zone=main¤tActivity=feed&usageType=outward&
6_version%3D1%26md5%3D2650e2112070d1587dc10446701c9c37

**From:** Michael Dourson <doursoml@ucmail.uc.edu>
**Date:** Thursday, February 23, 2017 at 2:28 PM
**To:** Akihiko Hirose <akihikoh@dranihs.net>, [Ex. 6] <[Ex. 6]>, "'Michael L. Caldwell'" <MCaldwell@zacfirm.com>, "Beck, Nancy" <Nancy_Beck@americanchemistry.com>, "Birchfield, Norman" <Birchfield.Norman@epa.gov>, yamazaki <k-yamazaki@jisha.or.jp>, "kmdilwali@intsci.com" <kmdilwali@intsci.com>, "'Michael L. Caldwell'" <MCaldwell@zacfirm.com>, "Pierre_Therriault@hc-sc.gc.ca" <Pierre_Therriault@hc-sc.gc.ca>, Richard Charron <Richard.Charron@hc-sc.gc.ca>, "Sams, Reeder" <Sams.Reeder@epa.gov>, Michael Honeycutt <MHoneycu@tceq.state.tx.us>, "Deshpande, Satish (MOECC)" <Satish.Deshpande@ontario.ca>, "Labib, Sarah (HC/SC)" <sarah.labib@canada.ca>, Shannon Ethridge <sethridg@tceq.state.tx.us>, Barbara Sassi <barbara.sassi@health.mo.gov>, Dennis Wambuguh <dennis.wambuguh@health.mo.gov>, Chris Prucha <cprucha@wm.com>, "h-kano@jisha.or.jp" <h-kano@jisha.or.jp>, Andy Maier <maierma@ucmail.uc.edu>, "t-kasai@jisha.or.jp" <t-kasai@jisha.or.jp>, "sethridg@tceq.state.tx.us" <sethridg@tceq.state.tx.us>, Robert Maronpot <maronpot@me.com>, "Whalan, John" <Whalan.John@epa.gov>, "Klaunig, James E." <jklauni@indiana.edu>, Jayne Wright <jayne@jaynewright.co.uk>, Nadine Weinberg <nadine.weinberg@erm.com>, "Garoutte, Jonathan" <Jonathan.Garoutte@health.mo.gov>, "Flaga, Christine (DEQ)" <FLAGAC@michigan.gov>, "Joseph.Haney@tceq.texas.gov" <Joseph.Haney@tceq.texas.gov>, "Phelka, Amanda" <aphelka@nsf.org>, "English, Joanne Caroline" <jenglish@nsf.org>, "Laessig, Susan" <Laessig.Susan@epa.gov>, "Herbert, Ron (NIH/NIEHS) [E]" <herbert@niehs.nih.gov>, "oono-yurie@mhlw.go.jp" <oono-yurie@mhlw.go.jp>, toxpathmcc <toxpathmcc@bellsouth.net>, "Jeff.Wenzel@health.mo.gov" <Jeff.Wenzel@health.mo.gov>, Maria Hegstad <mhegstad@iwpnews.com>, Doug Wolf <Wolf.Doug@epamail.epa.gov>, "Goeden, Helen (MDH)" <Helen.Goeden@state.mn.us>, "Kelly, James (MDH)" <james.kelly@state.mn.us>, "Franz, Christina" <Christina_Franz@americanchemistry.com>, Kylie Brockenfelt <KBrockenfelt@epl-inc.com>, "Ries, Divinia (DEQ)" <RIESD@michigan.gov>, "'Sager, Shawn'" <Shawn.Sager@arcadis.com>, "HOWARD, WILLIAM B GS-13 USAF AFMC AFCEC/CZTE" <william.howard.40@us.af.mil>, "Hamlin, Mel (NIH/NIEHS) [C] (hamlin@niehs.nih.gov)" <hamlin@niehs.nih.gov>, "ruckner@rx.uga.edu" <ruckner@rx.uga.edu>, Harvey Clewell <HClewell@thehamner.org>, "david_dorman@ncsu.edu" <david_dorman@ncsu.edu>, "fjmiller@nc.rr.com" <fjmiller@nc.rr.com>, "rpsharma@uga.edu" <rpsharma@uga.edu>, John Vandenberg <Vandenberg.John@epamail.epa.gov>
**Cc:** "'Higginbotham, Jeri ' (EEC)" <Jeri.Higginbotham@ky.gov>, "jcrum@hampmathews.com" <jcrum@hampmathews.com>, "'Burleigh-Flayer, Heather'" <burleighflayer@ppg.com>, Patricia Nance <nancepm@ucmail.uc.edu>, "'Forsberg, Norman'" <Norman.Forsberg@arcadis.com>, 'Mark Lafranconi' <Mark.Lafranconi@erm.com>
**Subject:** Accepted 1,4-Dioxane Publication

Dear Colleagues

On behalf of the authors listed in the CC section of this email, it gives me great pleasure to state that a manuscript entitled "Update: Mode of Action (MOA) for Liver Tumors Induced by Oral Exposure to 1,4-Dioxane" has been accepted by Regulatory Toxicology and Pharmacology. An abstract is found below.

This work was conducted under the auspices of the Alliance for Risk Assessment (*ARA*), and involved multiple groups acting collaboratively. Updates of this accepted text prior to it being published will be posted on the Alliance for Risk Assessment (*ARA*) website, specifically, http://allianceforrisk.org/14-dioxane-analysis.

Please feel free to let your colleagues know as well.

Sincerely,

Michael L. Dourson, Ph.D., DABT, FATS, FSRA
Professor
Risk Science Center (formerly TERA)

Department of Environmental Health
University of Cincinnati, College of Medicine
160 Panzeca Way
Cincinnati OH 45267-0056

michael.dourson@uc.edu
513-558-7949
Ex. 6

http://eh.uc.edu/tera/


**Abstract**
Previous scientific studies show that the weight of evidence supports the hypothesis that 1,4-dioxane causes liver tumors in rodents through cytotoxicity and subsequent regenerative hyperplasia. Questions regarding a lack of concordant findings for this mode of action (MOA) in mice have not been resolved, however. In the current work, a reanalysis of data from two chronic mouse cancer bioassays on 1,4-dioxane, one 13-week mouse study, seven rat cancer bioassays, coupled with other data demonstrating negative mutagenicity, lack of up-regulated DNA repair, and the appearance of liver tumors with a high background incidence, support the conclusion that rodent liver tumors, including those in mice, are evoked by a regenerative hyperplasia MOA. The initiating event for this MOA is metabolic saturation of 1,4-dioxane. Above metabolic saturation, higher doses of the parent compound cause an ever increasing toxicity in the rodent liver as evidenced by higher blood levels of enzymes indicative of liver cell damage and associated histopathology that occurs in a dose and time related manner. Importantly, alternative modes of action can be excluded. The observed liver toxicity has a threshold in the dose scale at or below levels that saturate metabolism, and generally in the range of 9.6 to 42 mg/kg-day for rats and 57 to 66 mg/kg-day for mice. It follows that threshold approaches to the assessment of this chemical's toxicity are supported by the non-mutagenic, metabolic saturation kinetics, and cytotoxicity-generated regenerative repair information available for 1,4-dioxane promoted rodent liver tumors.

**From:** eesserver@eesmail.elsevier.com [mailto:eesserver@eesmail.elsevier.com]
**Sent:** Thursday, February 23, 2017 10:33 AM
**To:** Nance, Patricia (nancepm) <nancepm@ucmail.uc.edu>; Ex. 6
**Subject:** RTP-16-335R2: Final Decision

Ms. No.: RTP-16-335R2
Title: Update: Mode of Action (MOA) for Liver Tumors Induced by Oral Exposure to 1,4-Dioxane
Corresponding Author: Ms. Patricia Nance
Authors: Michael Dourson; Jeri Higginbotham; Jeff Crum; Heather Burleigh-Flayer; Norman Forsberg; Mark Lafranconi

Dear Ms. Nance,

Congratulations. I am pleased to inform you that your manuscript, referenced above, has been accepted for publication in Regulatory Toxicology and Pharmacology.

Many thanks for this paper. We look forward to the submission of your future manuscripts to Regulatory Toxicology and

Pharmacology.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

When your paper is published on ScienceDirect, you want to make sure it gets the attention it deserves. To help you get your message across, Elsevier has developed a new, free service called AudioSlides: brief, webcast-style presentations that are shown (publicly available) next to your published article. This format gives you the opportunity to explain your research in your own words and attract interest. You will receive an invitation email to create an AudioSlides presentation shortly. For more information and examples, please visit http://www.elsevier.com/audioslides.

With kind regards,

Dr. Gio Batta Gori, Editor-in-Chief
Regulatory Toxicology and Pharmacology
E-mail: rtp@elsevier.com

Message (Digitally Signed)

**From**: Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]
**Sent**: 5/18/2018 5:54:07 PM
**To**: Underwood, Patricia M CIV (US) [patricia.m.underwood.civ@mail.mil]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Christopher.Weis@nih.gov; Cibulas, William Jr CAPT USPHS (US) (wic1@cdc.gov) [wic1@cdc.gov]; Bill Perry (perry.bill@dol.gov) (perry.bill@dol.gov) [perry.bill@dol.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Kimberly_White@americanchemistry.com; Michael Dourson [dourson@tera.org]; Ken Olden Ex. 6; Johnson, Mark S CIV USARMY MEDCOM APHC (US) [mark.s.johnson.civ@mail.mil]; Hutchens, Sherri L CIV USARMY MEDCOM APHC (US) [sherri.l.hutchens.civ@mail.mil]; Sorrentino, Claudio@DTSC [Claudio.Sorrentino@dtsc.ca.gov]; Seibert, John F CIV OSD OUSD ATL (US) [john.f.seibert.civ@mail.mil]
**CC**: 'George Gray' [gmgray@gwu.edu]; Rak, Drew [andrew.rak@noblis.org]; Anita.K.Meyer@usace.army.mil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ebb41195f2324548959139e28c25b8a6-Anita.K.Meyer@usace.army.mil]; Scanlon, Kelly A CIV OSD OUSD ATL (US) [kelly.a.scanlon4.civ@mail.mil]
**Subject**: RE: Roundtable Discussion on Developing High Quality Human Health Reference Values for Use in Exposure Scenarios of Primary Interest to DoD - Save the Date June 26, 2018 (UNCLASSIFIED)
**Attachments**: smime.p7s

Tricia
I would love to participate. Please sign me up.

Many thanks.

Linda

Linda S. Wennerberg, Ph.D.
Environmental Management Division
NASA Headquarters
MS-2T89
300 E Street SW
Washington, DC 20546-0001

Tel: 202/358-4558
Cell: Ex. 6
Fax: 202/358-3948
linda.s.wennerberg@nasa.gov

-----Original Message-----
From: Underwood, Patricia M CIV (US) [mailto:patricia.m.underwood.civ@mail.mil]
Sent: Friday, May 18, 2018 1:34 PM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Christopher.Weis@nih.gov; Cibulas, William Jr CAPT USPHS (US) (wic1@cdc.gov) <wic1@cdc.gov>; Bill Perry (perry.bill@dol.gov) (perry.bill@dol.gov) <perry.bill@dol.gov>; Seifert, Robert <Robert.Seifert@EM.Doe.Gov>; Wennerberg, Linda S. (HQ-LD020) <linda.s.wennerberg@nasa.gov>; Kimberly_White@americanchemistry.com; Michael Dourson <dourson@tera.org>; Ken Olden Ex. 6; Johnson, Mark S CIV USARMY MEDCOM APHC (US) <mark.s.johnson.civ@mail.mil>; Hutchens, Sherri L CIV USARMY MEDCOM APHC (US) <sherri.l.hutchens.civ@mail.mil>; Sorrentino, Claudio@DTSC <Claudio.Sorrentino@dtsc.ca.gov>; Seibert, John F CIV OSD OUSD ATL (US) <john.f.seibert.civ@mail.mil>
Cc: 'George Gray' <gmgray@gwu.edu>; Rak, Drew <andrew.rak@noblis.org>; Meyer, Anita K CIV USARMY CEHNC (US) <Anita.K.Meyer@usace.army.mil>; Scanlon, Kelly A CIV OSD OUSD ATL (US) <kelly.a.scanlon4.civ@mail.mil>
Subject: Roundtable Discussion on Developing High Quality Human Health Reference Values for Use in Exposure Scenarios of Primary Interest to DoD - Save the Date June 26, 2018 (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

Colleagues:

I would like to invite you to participate in a roundtable discussion on June 26, 2018 that will be facilitated by Dr. George Gray at the Milken Institute School of Public Health at George Washington

University .  The discussion will center around the Department of Defense interests to establish a process for developing human health reference values (HHRVs) to support environmental and occupational health decision making.  These HHRVs will often be for chemicals or exposure scenarios of primary interest to DoD although they will be shared and made part of the wider "commons" of toxicology values. DoD desires a robust, rigorous and replicable process to ensure the credibility of these HHRVs and their broader utility.

The purpose of this initial discussion is to gather perspectives and experiences,  share lessons from other HHRV processes, identify specific challenges and best practices, and design a follow on workshop to help DoD develop a process.

I value the perspective and expertise you bring to the topic and hope you will be able to participate. Please feel free to contact me with any questions or feedback that may be of use as we work toward developing our agenda.

An outlook invitation with additional logistical details will be forthcoming within the next week.

Best regards,
Tricia

Patricia Underwood, PhD, DABT, MBA
Deputy for Chemical and Material Risk Management
Office of the Deputy Assistant Secretary of Defense
(Energy, Installations & Environment) ESOH
4800 Mark Center Drive
Box#56, Suite 17D08
Alexandria, VA 22350

Ph:703-901-8747

CLASSIFICATION: UNCLASSIFIED

Message

**From**: McClintic, Howard [McClintH@ctc.com]
**Sent**: 4/20/2018 9:55:42 PM
**To**: Ex. 6 [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8e5cafd35ee842ecb3d96d25c2d7dfc2-rgolden124@aol.com]; Alex Beehler Ex. 6; Charles Rigler (Charles.Rigler@charleskochinstitute.org) [Charles.Rigler@charleskochinstitute.org]; grizzle@grizzleco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=607f0c9ada1547d0b72901f88202889c-grizzle@grizzleco.com]; Mike Holmes (MikeHolmes@lignite.com) [MikeHolmes@lignite.com]; Jason Bohrer (JasonBohrer@lignite.com) [JasonBohrer@lignite.com]
**Subject**: Senate votes to kill consumer bureau auto-lending restrictions

Many of us will remember our discussions of the 1996 Congressional Review Act at the US Chamber– the trigger was pulled this week in the Senate -- historic!
https://www.uschamber.com/sites/default/files/9.7.17 - _testimony_to_senate_hsgac_subcommittee_on_hearing_on_permit_streamlining_and_fpisc.pdf

https://www.politico.com/story/2018/04/18/senate-votes-to-kill-consumer-bureau-auto-lending-restrictions-492328?cid=apn

# Senate votes to kill consumer bureau auto-lending restrictions

By ZACHARY WARMBRODT
04/18/2018 01:30 PM EDT

The Senate on Wednesday moved to eliminate a 2013 consumer protection measure intended to combat discrimination in auto lending, marking an expansive new use of its power to kill federal regulations.

The lawmakers voted 51-47 to gut the Consumer Financial Protection Bureau's guidance, which Republicans attacked as harmful to auto dealers and lenders. The House is expected to pass the measure soon, and President Donald Trump will likely sign it.

The consequences of the vote will ripple beyond the confines of the CFPB, which is already on a deregulatory path under the leadership of Mick Mulvaney, Trump's White House budget chief.
**It was the first time the Senate has used its authority under the 1996 Congressional Review Act to strike down an action taken by an agency years ago**, instead of just within the narrow window prescribed by the law. **The move also marked a broadening of how Congress has generally used the Review Act to include regulatory guidance and not only formal agency rules that were recently issued.**

"It's important for Congress to reassert its role in policymaking from the executive branch," said Sen. Jerry Moran (R-Kan.), who introduced the bill that would undo the regulation. Consumer advocates warn that the maneuver could expose decades of regulatory actions to being struck down by Republicans and Trump.

The CFPB guidance that Republicans targeted Wednesday outlines safeguards that lenders should follow to address racial discrimination by auto dealers, which often have a say in the terms for car loans because they facilitate financing for car buyers.

GOP lawmakers argued that it was unfair to dealers and the finance industry and underwent a flawed drafting process.
“If this rule stands, banks, credit unions and finance companies holding nearly $1.1 trillion in outstanding loans will needlessly face significant liability and the ability of auto dealers to play a valuable role by matching buyers and lenders will be diminished,” Senate Banking Chairman Mike Crapo (R-Idaho) said.

Republicans employed a fast-track procedure that allowed them to sidestep a filibuster by Democrats, who have generally resisted efforts to chip away at the bureau and fought attempts to repeal anti-discrimination regulations.

Sen. Joe Manchin (D-W. Va.) was the lone Democrat to vote in favor of the rollback, though others in his party were on the fence until shortly before the first procedural vote on the bill Tuesday.
Manchin said he didn’t see evidence in his state of a problem with discrimination by auto dealers.
“I have a great relationship with all the car dealers back in the state of West Virginia, and I have checked with every one of them,” Manchin said in an interview. “If I thought that any one of them — and these are people I've known all my life — would ever discriminate against anybody, for any reason whatsoever, I would have been coming after them. I’ve never had a complaint on that, never once."

The turnout by Democrats was in stark contrast to last month, when 17 members of the caucus voted for an even more wide-ranging bank deregulation bill that exposed them to aggressive, personal attacks from the left.

Progressives kept a close eye on the vote Wednesday to gauge whether they had sufficiently scared Democrats away from supporting more rollbacks of financial regulations.

Opponents of the bill warned of long-lasting impacts on federal regulation in the wake of the vote.

**While Republicans under Trump have used the Congressional Review Act to overturn more than a dozen rules, the Senate broke new ground by using the law to undo a federal agency guidance document that had not gone through formal rulemaking procedures.**

**Agencies often issue informal guidance to advise businesses and other stakeholders about how laws and rules are being interpreted. In this case, Republicans said the CFPB went beyond simply clarifying its view on existing law.**

**Sen. Pat Toomey (R-Pa.), who orchestrated the effort, was able to bring the CFPB guidelines under the scope of the Review Act by asking the Government Accountability Office to determine that they amounted to a "rule" for the purposes of the law.**

**The GAO determination in December opened a brief window for Republicans to undo the guidance, thanks to time-limited fast-track authority under the Congressional Review Act that allowed them to escape a filibuster by Democrats.**

The Republicans could reset the clock on other agency actions from past years that weren't submitted to Congress as formal rules by asking the GAO to make the same determination.

Democrats and consumer advocates warned that the maneuver set **a dangerous precedent that could put a wide universe of regulatory actions at risk and have a lasting impact on how agencies craft rules.**
**"They can go back 20 years," said Sen. Sherrod Brown of Ohio, the top Democrat on the Senate Banking Committee.**

Republicans argued they were keeping the federal bureaucracy accountable. In the case of the CFPB, they said the bureau did not follow Administrative Procedure Act requirements to take formal notice and comment in a significant regulatory action. They also said the bureau is legally prohibited from regulating auto dealers. The guidance was addressed to lenders that fall under the CFPB's jurisdiction.

Some of the Democrats who opposed the rollback co-sponsored a 2008 bill that would have blocked a directive from the Center for Medicare and Medicaid Services that, like the CFPB guidance, was not crafted under the formal rulemaking requirements of the APA.
The Senate didn't pass the bill, but Republicans used it this week to bolster their case.

"The use of the Congressional Review Act to repeal a guidance is well-established," Toomey said. "It is consistent with any plain reading of the law. It is consistent with the intent of the authors at the time. Congress has attempted to do so in the past. Democrats have attempted to do it."

Unlike 2008, when Democrats were fighting a Republican president, the GOP Wednesday has a clear path to roll back regulations thanks to control of Congress and the White House. Toomey said there was "no evidence" that the floodgates of repeal would be opened as critics warned this week. But he added that "any guidance, in fact any rulemaking, I think ultimately should be subject to congressional review because, after all, it's our authority in the first place that is used to generate it."

Consumer advocates warn that the maneuver could expose decades of regulatory actions to being struck down by Republicans and Trump.

The CFPB guidance that Republicans targeted Wednesday outlines safeguards that lenders should follow to address racial discrimination by auto dealers, which often have a say in the terms for car loans because they facilitate financing for car buyers.

Message

**From:** Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
**Sent:** 10/13/2017 11:00:32 PM
**To:** mwhittaker@toxservices.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f63b7262223e4c33a1ca6606254d1372-mwhittaker@toxservices.com]
**CC:** Jennifer Tanir [Ex. 6]; Richard E. Engler, Ph.D. [rengler@lawbc.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; Devito, Steve [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=be78622515bd451e96e948786357fb45-SDevito]; Henry, Tala [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8bfc0a617a4a43baa8856541c70622be-THENRY02]; Kimberly_White@americanchemistry.com; [Ex. 6]; Ashley Black [ashley@toxicology.org]
**Subject:** Re: Thanks to each of you--Oct 13 NCAC/CSW symposium

Meg,
Thanks to you and NCAC/ACS team for putting together such a nice program. I only wish I could have stayed for the full day.

I hope it was a success and I look forward to further dialogue-- it's important for the success of our programs.

Regards,
Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: [Ex. 6]
Beck.Nancy@epa.gov

On Oct 13, 2017, at 6:22 PM, Margaret Whittaker <Mwhittaker@toxservices.com> wrote:

> Thanks to everyone for presenting at today's symposium. I am very appreciative of the time that each of you took to prepare and participate.
> I hope everyone has a nice weekend!
> Sincerely,
> Meg

Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC
1367 Connecticut Avenue, N.W., Suite 300
Washington, D.C. 20036
(202) 429-8787 (US telephone)
+44(0) 20 3318 3429 (UK telephone)
(202) 429-8788 (fax)
www.toxservices.com

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**From:** Jennifer Tanir [Ex. 6]
**Sent:** Thursday, October 12, 2017 12:03 PM
**To:** beck.nancy@epa.gov; Richard E. Engler, Ph.D. <rengler@lawbc.com>; jsass@nrdc.org; Steve Devito <Devito.Steve@epa.gov>; Henry.Tala@epa.gov; Kimberly_White@americanchemistry.com; [Ex. 6]
**Cc:** Margaret Whittaker <Mwhittaker@toxservices.com>; Ashley Black <ashley@toxicology.org>
**Subject:** Re: Important details about Oct 13 NCAC/CSW symposium

Dear Presenters,
Please send me your presentations, short bios, and SOT permission form (attached) by this afternoon. The attached table summarizes the materials I've received so far.

Tomorrow's program starts early, so we would like to have everything in place by later today. Also, SOT will be running and recording a live webinar during the symposium, so we need to make sure we have the permissions in place in advance.

If you have any questions, please don't hesitate to contact me anytime! My cell is [Ex. 6] It should be an excellent symposium!

Thanks,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary

On Fri, Oct 6, 2017 at 9:36 AM, Jennifer Tanir [Ex. 6] wrote:

> I knew I would forget something! I meant to also ask you to send a **short bio** with your slides, so we can properly introduce you. Meg and I know who you are, but a few sentences will help us get the details right, and can avoid Meg telling some embarrassing story about you :)
>
> Thanks!
> Jen
>
> On Fri, Oct 6, 2017 at 8:18 AM, Jennifer Tanir [Ex. 6] wrote:
>
> > Dear presenters,
> > Our symposium is just a week away! Thank you so much for agreeing to participate. I have a few deadlines and details to let you know about:
> >
> > **Presentations:** please provide your presentation to me by **Wednesday, October 11**. The reason is that we are running a webinar of the symposium from SOT headquarters during the live event at ACS headquarters, so we need to copies in both places and make sure they're working. If you have trouble meeting this deadline, please let me know.

**Permission:** please **fill in and return** the attached SOT permission form regarding release of your materials. The webinar will be recorded and posted on the SOT website, along with the slides, pending your permission. If you have questions, please contact Ashley Black at SOT (cc'ed).

**Agenda:** the final symposium agenda is located here: https://www.toxicology.org/groups/rc/ncac/docs/NCAC_CSW_Fall_2017_Symposium_Final_Agenda.pdf.

**Registration:** you've all been registered for the meeting and received a confirmation email yesterday. Lunch and breaks are included (but no breakfast).

**Numbers/Set-up:** as of yesterday, we have 50+ people registered to attend in person and 40+ registered for the online webinar. The limit in the room will be about 75 people (set 6-8 people around tables). The room is a long rectangle, with stage, podium, microphone, and large screen for your presentation, and additional TV screens towards the back of the room for viewing of the slides. In a side room, we'll have 24 posters by students & postdocs during the poster competition. We'll take questions from the "chat window" of the webinar too, during the Q&A periods.

Please let me or Meg know if you have any questions as you prepare for the symposium!

Best,
Jen

Jennifer Y. Tanir, PhD
CSW Secretary
**Ex. 6**


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Message

**From**: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
**Sent**: 9/26/2017 3:57:18 PM
**To**: Bridgeford, Tawny [TBridgeford@nma.org]
**CC**: Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Clark, Sharon [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6821d9dde270456caa67a7114e49f707-Clark, Sharon]
**Subject**: RE: Invitation to Speak at NMA's Environment Committee Meeting in October

Tawny,
You will be in great hands with Jeff. I've cc'd him above so you have his contact information. Sharon Clark is also cc'd and she can assist with Jeff's schedule to find a workable time.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Bridgeford, Tawny [mailto:TBridgeford@nma.org]
**Sent:** Tuesday, September 26, 2017 10:26 AM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Cc:** Hanley, Mary <Hanley.Mary@epa.gov>
**Subject:** RE: Invitation to Speak at NMA's Environment Committee Meeting in October

Thanks Nancy! Sorry for the delayed response. I have been out of the office on travel. Should I work with Mary on the scheduling? Or contact Jeff directly? If Jeff, would you mind connecting me to him as we have not previously met.

Best,

Tawny

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, September 22, 2017 9:40 AM
**To:** Bridgeford, Tawny <TBridgeford@nma.org>
**Cc:** Hanley, Mary <Hanley.Mary@epa.gov>
**Subject:** RE: Invitation to Speak at NMA's Environment Committee Meeting in October

Hi Tawny,

I hope you are well. I will be out of the office the week before on travel so I've asked Jeff Morris to cover this one. He and his TRI experts are likely going to be the most helpful to you and your members.

Regards,
Nancy

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Bridgeford, Tawny [mailto:TBridgeford@nma.org]
**Sent:** Tuesday, September 19, 2017 2:10 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** Invitation to Speak at NMA's Environment Committee Meeting in October

Nancy:

On behalf of the National Mining Association, I am writing to invite you to speak at our Environment Committee meeting on Oct. 16 or 17, 2017, in Washington, D.C. Details regarding the meeting are in the attached formal invitation. We look forward to hearing from you or your staff!

Regards,

Tawny

Tawny Bridgeford
Deputy General Counsel & Vice President, Regulatory Affairs
National Mining Association
101 Constitution Ave, NW, Suite 500 East
Washington, D.C. 20001
Phone: (202) 463-2600
Direct: Ex. 6
tbridgeford@nma.org

Message

**From**: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
**Sent**: 8/4/2017 6:53:13 PM
**To**: Jain, Komal [Komal_Jain@americanchemistry.com]
**Subject**: RE: hiring?

Ok. definitely send a CV. There is a hiring freeze (unless he wants to be a fellow ☺) so I think political is the most workable.

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Jain, Komal [mailto:Komal_Jain@americanchemistry.com]
**Sent:** Friday, August 4, 2017 2:45 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** RE: hiring?

He would certainly consider it.

**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
**Sent:** Friday, August 4, 2017 2:38 PM
**To:** Jain, Komal <Komal_Jain@americanchemistry.com>
**Subject:** RE: hiring?

Hey Komal,
Would he take a political position?

---

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

**From:** Jain, Komal [mailto:Komal_Jain@americanchemistry.com]
**Sent:** Friday, August 4, 2017 2:35 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** hiring?

Hi Nancy,

I hope you are doing well. Busy for sure! I'd love to catch up whenever you can clear your calendar for lunch or a cocktail.

I heard through Seth Goldberg that you may be hiring for several positions. I'm not inquiring for myself, but for Ex. 6

Ex. 6

Ex. 6

Ex. 6 He's looking for senior level position in a policy/management role (not a scientist). Anything come to mind? I can shoot his CV over if there is a possibility.

Thanks! And, Happy Friday.

All the best,
Komal

*Komal K. Jain, J.D.* | American Chemistry Council
Senior Director, Chemical Products & Technology Division
komal_jain@americanchemistry.com
700 2nd Street, NE | Washington, DC | 20002
o: Ex. 6
m: Ex. 6


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