Im flying most of the day on Friday so I cant make the call.

On Jul 9, 2017, at 11:34 AM, jerryheindel <jerryheindel@gmail.com> wrote:

Open to all ideas. We will have another call at 1pm edit Friday

On Jul 7, 2017, at 7:42 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Thanks everyone. but it sure would be helpful to get more guidance on the people to invite, do we have the right ones, the best ones, do they cover all the important topics and the topics to discuss, we really need to define the list of 6-8 key topics to discuss. Then we can decide who among us will be responsible for developing each topic/session.

I cant invite anyone until we have a better flushed out program. Please take another look. Also comment on the meeting introduction/goal that is key. I know everyone has a
day job but I really need more help for this to be successful. Just take 15 minutes to go through the attachment and add comments like you were reviewing a paper. Thanks, jerry.

Sent from Mail for Windows 10

From: R. Thomas Zoeller
Sent: Thursday, July 6, 2017 3:57 PM
To: jerry heindel
Cc: Fred Vomsaal; Hunt, Pat; Pete Myers; Bruce Blumberg; Amy Kostant; Joe DiGangi
Subject: Re: December EDC meeting: response needed

Hi Jerry and all I agree with what Fred is saying. We can think of a lot of people, and we dont know what the response rate will be. Like over-selling airline seats. A couple of additional thoughts.

First, Im thinking of how policy should direct research and vice versa. I think it is true that research in this field has improved in terms of refining experimental design and questions to inform policy. [note: policy here means how individual chemicals are evaluated and risk assessed. Larger questions of laws, rules and processes are larger and need to be evaluated separately]. However, I dont see that policy at either level has been terribly responsive to new research. Rather, it seems like regulatory agencies have gotten better at saying how they follow sound science without actually incorporating relevant science. It might be good to have an NGO represented (maybe TEDX can do this) to talk about the large and small questions of policy<->science interplay?

The other avenue of affecting change is through public awareness/industry awareness. There should be some discussion of this issue broadly and how we can collectively interact with industry both to help them navigate the complexity of producing safer products, but also to help them communicate truthfully.

Finally, something that Joe Laakso might help with. This article made me wonder whether this is something we could emulate. https://www.nytimes.com/2017/07/04/opinion/putting-citizenship-back-in-congress.html? r=0

Tom

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA  01003

ph:       (413) 545-2088
Fax: (413) 545-3243
On Jul 5, 2017, at 2:56 PM, jerry heindel <jerryheindel@gmail.com> wrote:

Hi all please look at the attachment and help me to fill in the detailslist of attendees to ask to attend and the list of main topics to discuss. Be sure there is expertise to cover the topics. Please respond by July 14th. Just write over the plan with your suggestions and send back.

It would be good to have a solid list of participants and draft program to send out by August 1 so people can plan. Thanks for your help. jerry
Sent from Mail for Windows 10

<Endocrine Disruption Strategies Workshop.docx>

<Endocrine Disruption Strategies Workshop.docx>
I would raise one caution about the direction this is headed. Once you go above 12-15 or so people the pooled intelligence of the group begins to decline. If you want really smart strategic thinking, this has too many people. We should also employ a filter examining who has disruptive traits that would interfere with group function.

On Jul 7, 2017, at 7:42 AM, jerry heindel <jerryheindel@gmail.com> wrote:

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Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

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It would be good to have a solid list of participants and draft program to send out by August 1 so people can plan. Thanks for your help. jerry

Sent from Mail for Windows 10

<Endocrine Disruption Strategies Workshop.docx>
Hi Emily,

Sorry for not getting back to you on this. Yes, this works for me. I will be at a meeting on the east coast but my afternoons will be free.

Pat

Hi Pat,
Terry said her preferred date would be Thursday, August 14th -- which means we would send our note to journalists either 8/7 or 8/11 -- does that work for you?

Best,
Emily

Hi Terry, Pat
We heard back from Prabha at ReproTox, and she said:

The proof will be sent to the author by 25th July 2014. If the author can return the author within 3 to 4 days, we should be ready with the corrected proof by the first week of August 2014. The timeline August 11 18, or mid-September through mid-October should be fine. Please let me know the date which you will prefer to release the article online.

If you both can decide which date youd prefer (and will both be available for press calls 5 days prior to publication date), well let Prabha know, and then inform the rest of the group working on media outreach. The August window is small, but there seems to be a much larger window starting mid-September.

Best,
Emily

Emily Copeland
I sent them to you yesterday morning.

Sent from my iPhone

On Dec 11, 2015, at 8:33 AM, "JPMyers@ehsic.org" <JPMyers@ehsic.org> wrote:

   I'd like to forward your original BPA-congression failure paper and the quat paper to David Montgomery.
we'll talk about this on SCN call tomorrow

as Rick pointed out, that soup contains 0 fat
huge confounding factor

Pete Myers, from a mobile phone

> On Jan 27, 2015, at 5:36 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:
> Hi Pete and Fred-
> You have probably both seen this but Lizzie Grossman just brought it to my attention. Tomato soup to coat the mouth? Now if they had used peanut butter.
> Pat - Teeguarden et al, 2015.pdf
> <Teeguarden et al, 2015.pdf>
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
To: Pete Myers <jpmyers@ehsic.org>
Sent: 4/21/2014 1:52:48 PM
Subject: Re: draft for Erik from NRDC

It could happen..

From: Pete Myers <jpmyers@ehsic.org>
Date: Monday, April 21, 2014 1:51 PM
To: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: Re: draft for Erik from NRDC

If I had one wish it would be that Pat Hunt would be my editor for eternity.

On Apr 21, 2014, at 4:39 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Here are my suggestions.

From: Pete Myers <jpmyers@ehsic.org>
Date: Monday, April 21, 2014 11:59 AM
To: Patricia Hunt <pathunt@vetmed.wsu.edu>
Cc: Laura Vandenberg <lvandenberg@schoolph.umass.edu>, Fred Vom Saal <vomsaalf@missouri.edu>, "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, "Hunt, Patricia Ann" <pathunt@wsu.edu>
Subject: Re: draft for Erik from NRDC

but bear in mind that this is one political person (Erik) talking to another (editor of Nature) about whether it's worth Nature's time to write an editorial and put a reporter onto this.
not a time for scientific niceties.

On Apr 21, 2014, at 3:57 PM, JPMyers@ehsic.org wrote:

that's why I sent it to you
please!

Pete Myers, from a mobile phone

On Apr 21, 2014, at 3:57 PM, "Hunt, Pat" <pathunt@vetmed.wsu.edu> wrote:

Hi Pete-

To me, the tone of this is a little harsh and the important points aren't coming through loud and clear. Mind if I work on it a bit?
Here is a draft of talking points for Erik to take to Nature. I tried not to go too far into the weeds but far enough so that Erik can make the first pitch and then steer the editor toward the four of you.

<2014-0421 FDA and BPA-ph.docx>
From: Patricia Hunt <pathunt@vetmed.wsu.edu>
To: Pete Myers <jpmyers@ehsic.org>
CC: Laura Vandenberg <lvandenberg@schoolph.umass.edu>, "Prof. Fred vom Saal" <vomsaalF@missouri.edu>, "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, "Hunt, Patricia Ann" <pathunt@wsu.edu>
Sent: 4/21/2014 2:39:12 PM
Subject: Re: draft for Erik from NRDC

Attach: [2014-0421 FDA and BPA-ph.docx]
Here are my suggestions.

On Apr 21, 2014, at 3:57 PM, JPMys@ehsic.org wrote:

that's why I sent it to you please!

Pete Myers, from a mobile phone

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but bear in mind that this is one political person (Erik) talking to another (editor of Nature) about whether it's worth Nature's time to write an editorial and put a reporter onto this.

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Here is a draft of talking points for Erik to take to Nature. I tried not to go too far into the weeds but far enough so that Erik can make the first pitch and then steer the editor toward the four of you.
Briefing for Nature Editor by Erik Olson

[Nature was a sponsor of the non-monotonicity workshop organized by Pew on April 20, 2012.]

Several recent actions by the US Food and Drug Administration suggest that FDA scientists and their ability to fairly and honestly communicate are being manipulative of the results of their research. Several recent actions by the US Food and Drug Administration raise concern about the objectivity of the FDA scientists’ ability to fairly and honestly communicate.

First, FDA scientists reached scientifically unsupportable conclusions in two related papers (Declos et al., 2014; Churchwell et al., 2014) on bisphenol A (BPA).

These papers report the findings of studies that were explicitly designed to test for low-dose effects, within a dose range reported by other scientists. The papers report no low-dose effects. In the discussion of the paper by Declos et al., the authors acknowledge that the negative controls used in the study were contaminated with BPA, with serum BPA concentrations comparable to those found in the four lowest dose experimental groups. Given this confounder, in the absence of uncontaminated negative controls, meaningful conclusions about the effects of low doses of BPA simply cannot be made. Not only is this a basic principal of experimental science, but it is the contention that the data from these studies provide any insight to the effects of exposure to low doses of BPA is untenable in view of the large body of published data demonstrating adverse effects at low doses.

Despite this fundamental flaw in their research, FDA scientists have actively promoted these results in print and radio interviews as confirmation of the safety of BPA.

Second, this issue is much larger than the publication of two scientifically flawed studies. Especially problematic because the findings published by Delos et al. and Churchwell et al. results are just one piece of a much larger collaborative study by the FDA and the National Institute of Environmental Health Sciences. As part of this collaborative initiative, other investigators involved in this collaborative study are taking samples obtaining tissues from animals exposed experimentally in the FDA laboratory and using analytical methods that are not only much more sensitive.
but also more relevant to endocrine-driven disease burdens such as diabetes, prostate cancer, and neurodevelopmental disorders).

The results of one such study that reports adverse effects on the developing brain caused by low doses of BPA have already been published, with adverse effects caused by low doses of BPA (Patisaul et al. 2012). Because this study was part of the collaborative effort, this study was reviewed and approved for publication by the FDA. Thus, senior FDA scientists involved in the BPA collaborative project unquestionably knew about the findings. Yet neither of these two manuscripts acknowledge its existence in their reference. This is highly inappropriate behavior in scientific publishing.

Third, the story doesn’t end with the publication of the Declos et al and Churchwell et al manuscripts: FDA scientists presented two abstracts at the March 2014 Society of Toxicology meeting. Both presenteding the results of gene expression studies measurements made of the siblings of the subject animals used in the Declos et al. and Churchwell et al. studies. Both abstracts also reported gain these find no low dose effects, results and, although not reported in the either abstracts, there are every reasons to believe that the negative controls in these experiments were also inadvertently exposed to BPA-contaminated. Further, according to experts on the tissues studied (prostate and mammary), flaws in the techniques used would bias the results toward the null, i.e., for both whole tissue was used, despite the fact that previous studies have identified the specific portions of the developing organ that are sensitive and should be selected for analysis. For prostate, the experimental design looked at the entire prostate, even though the prostate lobe is easiest to dissect and most likely to be found/used by people without extensive prostate experience is not sensitive to estrogens. For mammary tissues, once again the FDA scientists looked at the gland as a whole. Prior research on gene expression in mammary tissues has consistently shown that it is crucial to measure stromal and ductal components separately.

Because of the fact that these two manuscripts and the two recent abstracts represent a small portion of the larger data set, it is just a small number of studies in a large series that will be published from this consortium effort over the next two years, we are puzzled about by the FDA’s efforts to draw attention to flawed negative results and its while failing to non-mention positive results from closely related work.

It may be important to examine the current push in light of decisions currently under consideration by the European Union on BPA (via EFSA) and on endocrine disruption more generally (via the European Commission). Negative results from a US agency could play a very important role in those processes.

Lastly, it is important to note that, as part of the funding arrangement behind the FDA-NIEHS collaborative effort, participating academic scientists were told that they should not be publicly critical of FDA scientific findings. This has
dampened the ability of some of the scientists with the most knowledgeable about this work to contribute to public discussions.
Yes, thanks, Jerry. You and Fred have raised excellent points. I will work on a revision today and tomorrow to incorporate your points and anything Tom or Pete have to add.

Roy and I truly appreciate both the support and guidance all of you have provided. I have been trying not to let this upset me, but it feels like NIEHS is trying to drive some of us from the field. What a shame it would be to lose Roy. He has so many other projects that he could easily decide to give up on this one!

Pat

You might say r56 or some other funding. That....don't limit to r56. If you get r56 you will have to get data and then resubmit and get rescared.
Here are a few thoughts. Good luck, Jerry

Sent from Mail for Windows 10

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Hi Fred, Pete, Tom, and Jerry-

I appreciated your comments this afternoon and tried to incorporate them into a draft letter. I thought it might be stronger coming just from me so I could comment more strongly on Roys abilities. It is still a bit rough and Roy wants to add a few more references to his recent papers, but it covers what I think are the major points. I would appreciate any suggestions you can provide.

With thanks,

Pat
Hi Everyone,

I'm not sure if I'm replying to the most recent note on this, but attached are some thoughts on the communications aspects of the meeting.

Amy

From: jerryheindel [mailto:jerryheindel@gmail.com]
Sent: Sunday, July 30, 2017 9:08 PM
To: Vomsaal, Frederick S.; R. Thomas Zoeller
Cc: Bruce Blumberg; Amy Kostant; Hunt, Pat; Pete Myers; Joe DiGangi
Subject: Re: EDC strategies, updated program and attendees...for discussion

No problem just a straw man

Sent from my T-Mobile 4G LTE Device

-------- Original message --------
From: "Vomsaal, Frederick S." <VomsaalF@missouri.edu>
Date: 7/30/17 9:02 PM (GMT-05:00)
To: "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, jerry heindel <jerryheindel@gmail.com>
Cc: Bruce Blumberg <blumberg@uci.edu>, Amy Kostant <amy@sciencecom.org>, "Hunt, Pat" <pathunt@vetmed.wsu.edu>, Pete Myers <jpmyers@ehsic.org>, Joe DiGangi <joe@ipen.org>
Subject: Re: EDC strategies, updated program and attendees...for discussion

One suggestion is not to have anyone give more than one talk I notice Linda Birnbaum was put as a speaker on 3 panels that is a mistake Linda is under tremendous political pressure and is NOT making decisions that are in the interest of the EDC community her motivation is to squash any dissent and keep her head down I have not problem with her giving one talk but suggest that we do not begin the meeting with her speaking anyone who had to deal with her at the last CLARITY meeting would understand my concern she was out of control and did everything possible to squash discussions that the FDA might not have liked.

We need to put some significant thought into what we think anyone who is going to be is a leadership position is going to discuss in relation to what we think are the critical issues that need to be discussed.
FOR EXAMPLE

What are the big health challenges in endocrinology that have not yet been examined through an EDC lens

Linda and Terry talking in this 60 min session make no sense to me. Terry should give a presentation but not about issues in endocrinology linda is a toxicologist not an endocrinologist.

Fred

From: Tom Zoeller <tzoeller@bio.umass.edu>
Date: Sunday, July 30, 2017 at 6:28 PM
To: jerry heindel <jerryheindel@gmail.com>
Cc: Bruce Blumberg <blumberg@uci.edu>, Amy Kostant <amy@sciencecom.org>, "Hunt, Pat" <pathunt@vetmed.wsu.edu>, Fred vomsaal <VomsaalF@missouri.edu>, Pete Myers <jpmyers@ehsic.org>, Joe DiGangi <joe@ipen.org>
Subject: Re: EDC strategies, updated program and attendees...for discussion

Here are some comments on the agenda. Look forward to the call.

Tom

Heres arlenes email: Arlene Blum <arlene@greensciencepolicy.org>

R. Thomas Zoeller, Professor

Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243
On Jul 30, 2017, at 4:58 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Thanks Bruce, I am not advocating a large group either just want to be sure we have representation by the groups we need. We have only 18 confirmed with another 8 that hope to attend if they can get funding and or clear their schedule. I can get a local pediatrician who works on EDCs and perhaps Amy knows people who can help get word to community groups. What kind of community groups are we talking about? Like the lions club or community research focused groups?

One example is the our local EDC-NC group will work with the NIEHS program on womens health that gets over 600 attendees to expand focus on EDCs and health with some talks, posters and booths.

Discussion focused on getting the word out to community groups would be good. jerry

Sent from Mail for Windows 10

From: Bruce Blumberg
Sent: Saturday, July 29, 2017 3:42 PM
To: jerry heindel; Amy Kostant; R. Thomas Zoeller; Hunt, Pat; Prof. Fred vom Saal; 'Pete Myers'; Joe DiGangi
Subject: Re: EDC strategies, updated program and attendees...for discussion

Program looks good, but I am NOT in favor of all of a sudden making this a large meeting. I thought that we were always shooting for 30-ish people.

For medical/professional, we need two parts of the medical community: OB/Gyn (represented by Linda) and also pediatricians - these are the folks who need to hear our message the most urgently. Other MDs will be good, too, but those 2 are definitely needed.
How about a session on how to get our message out to community groups, with a few of them represented?

Bruce

On 7/29/2017 6:03 AM, jerry heindel wrote:

I made significant changes since we might have a smaller group. See what you think. We could also perhaps ask a few more key people who live close and could attend and contribute. Some basic researchers at NIEHS? Local EDC researchers who are clinicians? There is also room for another discussion topic see which one is not covered that needs to be.

Another topic Heather has offered to see if she could get us a conference room at NCSU if we don't have breakouts that might work but we would need 7-8 cars to drive people from hotel to NCSU and back each day we would save money. Think about that. jerry

Talk to you all next week Wednesday at 1 pm or before if you want to chat. jerry

Sent from Mail for Windows 10
Introduction/Goal:

The EDC topic is particularly challenging because it cuts across many disciplines from molecular physiology and endocrinology to genetics and personalized medicine, evolution and population ecology and economics and sociology. Studies of EDCs have and will continue to provide key data that can improve human and environmental health but the impact on health will only be as successful as we are at communicating the findings and implications to clinicians, the general public as well as chemists, lawyers, regulators and policy makers. Many people and working groups have become interested in the effects of EDCs including but not limited to the important work of SCN and EHN, CHE, TEDX, EDCfree and others in the NGO community, the Endocrine Society and many more around the globe. The study of EDCs has required that new biological insights are identified in parallel in a number of different fields. We propose that the EDC field as a whole, including scientific understanding and its impact on disease burden could be strengthened by the development of a yearly Forum that increases communication and collaboration across disciplines.

The goal of this workshop is thus to set up a yearly forum to help identify strategic needs and opportunities to advance the field and encourages strategic collaborations. This forum will provide a platform to define the critical issues facing the field, and develop plans to improve knowledge sharing, coordination and collaboration that will reduce the impact of EDC exposures on human health and improve the impact of EDC science on the regulation of EDCs.

The initial meeting will focus on key areas important to the EDC field. The focus will be refined and sharpened over the coming months, but might include efforts to bolster consumer interest in safer products, collaboration with chemists on chemical design, identify research needs and opportunities, improved coordination/collaboration among NGOs and regulatory and policy needs and coordination with lawyers around opportunities to foster change through litigation. There are specific needs in the EU centered around EDC regulations/guidelines and in the US centered around the Administration’s focus on undermining environmental policies and the emergence of science deniers. The field also needs to build/strengthen ties between medical professional groups whose health goals are impaired by EDCs. The general goal is to “see” where the field is, how it got there and how to move forward to improve our ability to reduce disease from environmental exposures. It will also focus on preparing for the next Forum which we propose will take place after the EDC Gordon Conference in Switzerland.

Planning Committee: Jerry Heindel, Pete Myers, Amy Kostant, Fred vom Saal, Bruce Blumberg, Tom Zoeller, Pat Hunt, Joe DiGangi

Commented [AK1]: I think the goal should be to identify strategic needs... and the yearly forum could be an outcome – perhaps in a sentence at the end of this paragraph.
Draft Program (still under construction)

Sunday evening, reception at Jerry Heindel’s House

Monday, December 4th

8:30 Welcome, introduction and overview of the meeting

8:45 Setting the Stage:
- What is in a name: Signal toxicity, metabolism disruptors, obesogens or EDCs Jun Kanno
- Significant impacts of EDCs on human health: major accomplishments/ how were they accomplished/lessons learned that will help future activities Tom Zoeller

10:00 General Discussion with Discussion Leaders
- (60 min) EDC research needs to improve impact of research/ new approaches/technologies (are we asking the right questions? : Pete Myers, Bruce Blumberg, Russ Hauser, Gail Prins)

Short Break

- (60 min) What are the big health challenges in endocrinology that have not yet been examined through an EDC lens and how might that happen? What is the next issue that needs to be developed?): Laura Vandenberg, Linda Birnbaum, Terry Collins

12:30 Lunch

1:30 General Discussion with Discussion Leaders
- (90 min) How do we develop a unified multinational response to attacks on scientific integrity from various sources: Pete Myers, Amy Kostant, Barbara Demeneix, Steve Tillery
- (75 min) Challenges/opportunities related to risk assessment, guideline studies and AOPs for EDCs: Shirlee Tan, Tom Zoeller, Heather Patisaul, Linda Birnbaum

Short Break

- (60 min) How to build/expand ties between medical professional groups whose health goals are impaired by EDCs: Linda Giudice, Loretta Doan, Joe Laasko

5:30 End for day...

Dinner at Hotel or restaurant at Crabtree Mall, (0.5 miles)

Tuesday December 5th

8:30 Overview: Are we asking the right questions, Pete Myers
9:00 **General Discussion**  How to improve the knowledge and acceptance of EDC data/principles/effects on human and wildlife health

- (45 min) How can scientists help NGOs/Societies? Sharyle Patton, Loretta Doan, Joe Laasko

- How do we expand into new avenues of communication, social media, infographics, etc: Sally Darney, Carol Kwiatkowski, Leo Trasande, Jane Muncke

**Short Break**

**Amy – infographics, twitter, fb**

(90 min) How to Communicate with and gain acceptance of scientific data by community, clinicians, science deniers? How do we change peoples’ thinking? What is the message we want to get out? : Amy Kostant, Linda Giudice, Barbara Demeneix

**Would be good to address:**

- What to say to NIH? Grantors? How to help NIEHS?
- Do we want to invite someone like George Lakoff to talk about framing? Example: Recently re: EPA Lakoff suggested that instead of “EPA regulations” we say “EPA protections.”

12:30 Lunch

1:45 Time for another plenary or discussion topic...ideas...what are we missing?

3:00 Break

3:20 **Plenary Session**: Moving Forward...General Discussion of next EDC Forum

- Can we develop working groups/focused workshops? Or listservs? What would be their purpose/goals?
- Plan for the next year’s meeting... Switzerland after Gordon Conference...need planning committee
- Discussion of meeting output

5:00 Workshop ends

(POSSIBLE) Attendees (by invitation only) Everyone pays all own expenses RED...NO, Blue no response, black yes or tentative

We could use more expertise in some areas even some in black are tentative

Jerry Heindel
Bruce Blumberg
Fred vom Saal
Tom Zoeller
Pat Hunt
Jodi Flaws

Commented [jh6]: We really need a few more NGOs
If not we can add another topic here

Commented [AK7]: To consider: NGO campaigns move more quickly than research is done. How to balance that so research will be most useful and campaigns can plan for the future?

Commented [AK8]: Sally could talk about working with journals – current and upcoming challenges, and how to help NIEHS; Carol could talk about webinars; Ken Cook should use EWG’s example of good use of social media. I’m not sure what Leo and Jane would cover: perhaps differences in EU/US press interest?

Commented [AK9]: To establish common understanding, SCN can provide a one-pager on definitions and some examples of the main ways social media is used to convey science

Commented [jh10]: Should invite someone with experience talking to science deniers...Amy knows people

Commented [AK11]: AK: I can invite someone to talk via skype (to keep it affordable), but I think we shouldn’t worry too much about deniers. I’ve been listening to/reading lots of experts, and this is mainly a big deal for climate, but for anything other than climate – if someone really doesn’t care, it’s pointless to argue. Instead we should focus on providing accurate, useful information to those who are somewhat interested or already engaged. Parents are a natural audience, and they are the perfect target for consumer campaigns. But they need accurate science to avoid alarmism and panic, and ultimately overload and ‘tuning out.’ If we reach parents with information they can use that isn’t overwhelming and terrifying, we will have strong allies. To do this we need to improve skills for talking with journalists; talking with community groups – make it local and about people (parent-to-parent); use of social media. And a research agenda can be cognizant of this key, huge, and ever-replenishing audience.
Kim Konte
Amy Kostant
Ted Schecter

**Expertise in Regulatory and Policy:** Pete Myers, Tracy Woodruff, Shirlee Tan, Heather Patisaul, Tom Zoeller, Joe Laasko, Joe DiGangi, Ken Cook, Linda Birnbaum

**Expertise in Green Chemistry:** Terry Collins

**Expertise in Communications:** Amy Kostant, Pete Myers, Carol Kwiatkowski, Tracy Woodruff, Karen Wang, Jeff Wise, Pat Hunt, Jane Muncke, Ken Cook

**NGO community/Scientific Societies:** EHN, EWG, TEDX, CHE, Endocrine Society, SCN, PHRE, Peds, Heal, Chemtrust, HEFN, community action groups, Mind the Store (safer chemicals: healthy families), Arlene Bloom, SEHN (Ted Schettler), EDF, Non toxic Irvine, Mamavation

**Expertise in Funding:** Shorey Myers, Pete Myers, Linda Birnbaum, Jeff Wise

**Expertise in legal matters:** Steve Tillery, Rena Steinzor

**Representative from EDC Gordon Conference Planning (June 2-8 Les Diablerets Switzerland):** Jodi Flaws

*Commented *[jh12]*: Few NGOs can afford to attend...too bad*
I agree with Pat, and know from personal experience that she rarely resists the urge to edit. So great job!

But I do have one suggestion. The discussion of cumulative exposure should be explicitly about the type of cumulative exposure to which it refers: different exposure types (food vs. air vs dermal, etc.) as opposed to cumulative exposure to different chemicals (i.e., mixtures).

On Jan 23, 2015, at 3:47 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

I agree that this is a very strong letter. I can almost never resist the urge to edit, but I sincerely think this is terrific as written.

I must admit that I am conflicted about adding other societies to this. It seems to me that this would be strongest coming from the Endocrine Society and I would hate to see the message diluted by trying to create a version that will represent a broader group of societies. I am eager to hear the thoughts of others on this. If a more inclusive letter is the consensus, I am happy to approach the Society for the Study of Reproduction, the Society for Developmental Biology, and the Am Society of Human Genetics but, if it were up to me, I'd leave it as an Endocrine Society response.

Nice work, Joe!

I concur with Andrea and applaud the effort. Thanks, Laura, for spearheading this.

Cheers,
Heather
On 1/21/2015 7:07 PM, Gore, Andrea C wrote:

   Hi Everyone,
   Im sorry I couldnt be on the call due to a conflict. I think this letter looks great.

   Andrea

Andrea C Gore, PhD
Johnson & Johnson Centennial Professor of Pharmacy
The University of Texas at Austin

[andrea.gore@austin.utexas.edu](mailto:andrea.gore@austin.utexas.edu)
[http://www.utexas.edu/pharmacy/divisions/pharmtox/faculty/gore.html](http://www.utexas.edu/pharmacy/divisions/pharmtox/faculty/gore.html)

On Jan 21, 2015, at 8:47 AM, Laakso, Joseph <jlaakso@ENDOCRINE.ORG> wrote:

   Dear All,

   Please find attached to this e-mail a draft response to the FDA Request for Comments on updates to the Redbook. I hope that I captured the concepts discussed during our conference call correctly. At this time I would welcome everyones input and suggestions on the draft. In order to give adequate time for Society committee review, followed by President Santens approval, I would appreciate your feedback on the letter on or before Monday, January 26.

   During the call, we discussed options to have other groups endorse the letter. Some of the language can be quickly and easily tweaked, should we ask for endorsements. After discussing process with staff at the Society, we suggest that formal requests for endorsements be made after presidential approval with the understanding that we will not be able to make additional changes to the letter at that point. This will ensure that we will be able to submit the letter before the Feb. 9 deadline. Therefore, please feel free to discuss the draft with interested colleagues at other organizations at this point if you think that we will need to make substantial revisions to the letter.

   Thank you very much for your help with this; I look forward to your feedback.

   Best regards,
   Joe
Dear All,

This is just a friendly reminder for our conference call this afternoon at 2:00 PM EST. Below, please see the items specifically requested by the FDA Request for Comment and some proposed topics that could guide our response. Also, please note the dial-in and meeting numbers. A link to the FDA RFC is provided here: LINK TO RFC

Many thanks,
Joe

The FDA has highlighted the following four questions for the public comment period:

1. What components of the Redbook should receive priority for review and update?
2. What aspects of the safety and risk assessment of food ingredients or other CFSAN-regulated products are not addressed and should be considered for incorporation in the Redbook?
3. How can the Redbook be updated to more fully support the development and submission of safety assessments for substances introduced into food?
4. How should we balance the desire for transparency and consistency in risk assessment as described in the Redbook, with the goal of flexibility in applying the most appropriate analysis for specific contexts?

In my discussion with Dr. Vandenberg, we thought that the Endocrine Society might be able to touch on some high-level endocrine concepts with a few specific examples. The following bullets are submitted for consideration:

- Encourage the FDA to consider appropriate endpoints for the evaluation of EDCs
- Highlight that GLP are not sufficient standards for the evaluation of EDCs
- Ask FDA to explicitly consider non-monotonic dose responses
Make suggestions for studies to appropriately consider critical time windows in development
Encourage the FDA to reach out to the Endocrine Society with questions

Access numbers:

North America Toll-free: 866-207-4782
International Toll Line: 1 205 278 5491
Meeting Number: *41*

Some toll-free options exist for international dialing. Please check below for your country.

- **Australia Toll Free**: 1800 189229
- **Australia Toll Free** (Optus): 1800 136961
- **Australia Toll Free** (Telstra): 1800 023406
- **Brazil Toll Free**: 8915323
- **Brazil Toll Free** (Embratel): 0800 8915323
- **Brazil Toll Free** (Telefonica): 0800 7612701
- **Denmark Toll Free**: 8088 9615
- **France Toll Free**: 0800 904662
- **Hungary Toll Free**: 0680 016692
- **Ireland Toll Free**: 1800 550005
- **India Toll Free**: 0008 001003766
- **Italy Toll Free**: 8008 71712
- **Netherlands Toll Free**: 0800 0221147
- **Norway Toll Free**: 8001 5281
- **Poland Toll Free**: 0080 01113927
- **Spain Toll Free**: 9009 57689
- **Sweden Toll Free**: 0207 99379
- **Switzerland Toll Free**: 0800 894853
- **UK Toll Free**: 0808 1016984
- **UK Toll Free (British Telecom)**: 0808 2344182

---

**From:** Laakso, Joseph  
**Sent:** Monday, January 12, 2015 5:15 PM  
**To:** JPMcMyers@ehsic.org; tzoeller@bio.umass.edu; drmvma@gmail.com; andrea.gore@austin.utexas.edu; Heather Patisaul (hbpatisa@ncsu.edu); blumberg@uci.edu; pathunt@wsu.edu; Laura N
Dear All,

Thank you very much for indicating your availability. At this time I would like to schedule the conference to discuss an Endocrine Society response to the FDA Redbook Request for Comments for this Friday, January 16, from 2:00 PM 3:00 PM EST. In advance of the call, I will be sure to circulate a link to the RFC and I would be happy to share any relevant background information with the group if you have any other suggestions. The dial-in and access numbers are below:

Access numbers:

North America Toll-free: 866-207-4782
International Toll Line: 1 205 278 5491
Meeting Number: *41

Some toll-free options exist for international dialing. Please e-mail jlaakso@endocrine.org for potential options if you will be dialing-in from outside north America.

Thank you very much, in advance, for your input and comments!

Best,
Joe
FDA will be holding a public meeting to collect comments on how it should update the Redbook. The purpose of our public meeting is to invite public input into possibly expanding the scope of the Redbook to include chemical safety assessments for all products over which FDA’s Center for Food Safety and Applied Nutrition (CFSAN) has statutory authority including regulatory contexts such as food additives, food contact substances, dietary supplement ingredients, food contaminants, and cosmetics. The FDA has highlighted the following four questions for the public comment period:

1. What components of the Redbook should receive priority for review and update?
2. What aspects of the safety and risk assessment of food ingredients or other CFSAN-regulated products are not addressed and should be considered for incorporation in the Redbook?
3. How can the Redbook be updated to more fully support the development and submission of safety assessments for substances introduced into food?
4. How should we balance the desire for transparency and consistency in risk assessment as described in the Redbook, with the goal of flexibility in applying the most appropriate analysis for specific contexts?

In my discussion with Dr. Vandenberg, we thought that the Endocrine Society might be able to touch on some high-level endocrine concepts with a few specific examples. The following bullets are submitted for consideration:

- Encourage the FDA to consider appropriate endpoints for the evaluation of EDCs
- Highlight that GLP are not sufficient standards for the evaluation of EDCs
- Ask FDA to explicitly consider non-monotonic dose responses
- Make suggestions for studies to appropriately consider critical time windows in development
- Encourage the FDA to reach out to the Endocrine Society with questions

These comments could also be used in any future meetings with the FDA to continue to emphasize a common and consistent set of positions and principles. At this time, I would like to help out by scheduling a conference call with those of us who might have time next week to discuss an Endocrine Society response in greater detail. If you have any availability within the following time windows (see below this e-mail), please let me know on or before this coming Sunday and I will go ahead and lock in a date/time that works for the maximum number of participants. If you are unable to participate in the call, please do not hesitate to reach out to me via e-mail or phone and I would be happy to work with you to ensure that your perspective is included in our comments.

Thank you very much,
Joe

(all times EST Conference Call will be scheduled for approximately 1 hour)
Monday, January 12
9:00 AM to 3:00 PM

Tuesday, January 13
9:00 AM to 12:00 PM
Or 1:00 PM to 5:00 PM

Wednesday, January 14
9:00 AM to 11:00 AM
Or
3:30 PM to 5:30 PM

Thursday, January 15
All day, 9:00 AM to 5:00 PM

Friday, January 16
1:00 PM to 5:00 PM

<Draft letter to FDA Regarding Redbook Update.docx>

--
Heather B Patisaul
Associate Professor
Department of Biology
NC State University
127 David Clark Labs
Raleigh NC 27695
919-513-7567
From: Pete Myers <jpmyers@ehsic.org>
To: "Karp, Harvey" <montee@earthlink.net>, "Prins, Gail" <gprins@uic.edu>, "Lanphear, Bruce" <blanphear@sfu.ca>, "Cranmer, Joan" <cranmerJoanM@uams.edu>, "Cory-Slechta, Deborah" <deborah_cory-slechta@urmc.rochester.edu>, Peter Orris <porris@uic.edu>, "Prof. Fred vom Saal" <vomsaalf@missouri.edu>, Terry Collins <tc1u@andrew.cmu.edu>, Howard Snyder <snyderh@email.chop.edu>, Peter DeFur <pldefur@igc.org>, "Ho, Shuk-mei" <shuk-mei.ho@uc.edu>, "Zoeller, Tom" <zoeller@bio.umass.edu>, "Prof. Louis J. Guillette" <lou.guillette@gmail.com>, Ted Schettler <tschettler@igc.org>, "Ozonoff, David" <dozonoff@bu.edu>, "Hayes, Tyrone" <tyrone@berkeley.edu>, "Woodruff, Tracey" <WoodruffT@obgyn.ucsf.edu>, "Dr. Steve Heilig" <heilig@sfms.org>, "Stahlhut, Richard" <richard_stahlhut@urmc.rochester.edu>, Sheldon Krinsky <sheldon.krinsky@tufts.edu>, Philip Landrigan <phil.landrigan@mssm.edu>, "Hunt, Pat" <pathunt@wsu.edu>, Shanna Swan <shanna.swan@mssm.edu>, "Russ Hauser" <rhauser@hohp.harvard.edu>, Bruce Blumberg <blumberg@uci.edu>, "Amy Kostant" <amy@sciencecom.org>, Bernard Weiss <Bernard_Weiss@urmc.rochester.edu>, Kalee Kreider <kaleekreider@gmail.com>, Laura Vandenberg <lvandenberg@schoolph.umass.edu>, Emily Copeland <emily@sciencecom.org>, Carl-Gustaf Bornehag <cguborn@kau.se>, "Michael Antoniou" <michael.antoniou@kcl.ac.uk>, Steve Gilbert <sgilbert@innd.org>, Leonardo Trasande <leonardo.trasande@nyu.edu>, Amy Itescu <itescu@UCMAIL.UC.EDU>
CC: "Gore, Andrea C" <andrea.gore@austin.utexas.edu>
Sent: 2/18/2015 5:09:33 AM
Subject: Re: Endocrine Society (and Andrea Gore) respond to WSJ editorial about Teeguarden study

Sorry. I forgot that WSJ stuff is behind a paywall. Here's the letter:

Endocrine Disruption and BPA Use

The preponderance of scientific evidence indicates that BPA presents a clear threat to public health.

February 18, 2015

Regarding your editorial "Snoopy Is Safe After All" (Feb. 12): The preponderance of scientific evidence indicates that bisphenol-A, known as BPA, and other endocrine-disrupting chemicals present a clear threat to public health.

As of 2014, nearly 100 epidemiological studies have been published linking BPA with human health problems, most notably disorders of reproduction, behavior and energy balance, according to the introductory guide to endocrine-disrupting chemicals published by the Endocrine Society and IPEN.

Despite this, the FDA continues to judge BPA using standards that have little relevance to endocrine disrupters. Unlike poisons, endocrine disrupters can have different—and often more insidious—effects at low levels
of exposure. The chemicals mimic, block or interfere with the body’s own hormones. Tiny amounts of these chemical messengers are enough to trigger significant biological changes, including birth defects during crucial stages of development.

The Teegarden study cited in your editorial wasn’t designed the same way as past animal studies and may have missed signs of immediate BPA absorption. Regardless of whether people digest BPA or absorb it in other ways, the Centers for Disease Control and Prevention have estimated that more than 96% of Americans have BPA in their bodies.

Finding a smoking gun linking a specific chemical to a particular disease is challenging because scientists cannot ethically expose humans to a toxic chemical. However, a wealth of evidence supports a direct link between BPA and a variety of health problems.

Regulators need to take into account the risks of low-dose exposure, particularly on unborn children, to effectively evaluate the dangers BPA poses.

Prof. Andrea C. Gore

University of Texas at Austin

Editor in chief of Endocrinology

Austin, Texas
Never mind! I just found it on the link to sign.

---

Hi All,

I am circulating this on behalf of Joe Allen as it may be of interest for you and your students:

Three graduate students from the Harvard T.H. Chan School of Public Health have written an article entitled "The Future of Environmental Health Is Now" to call our political leaders to action on stronger environmental health protections. This article, from the perspective of the current student generation, is part of The Environmentalist Papers series spearheaded by Dr. Joseph Allen at Harvard. We would like to invite your students to sign their names onto the article using this link.

Schools successfully reached so far:

1. Harvard University
2. University of Southern California
3. University of Washington
4. New York University
5. University of Michigan
6. Rutgers University
7. Columbia University
8. University of Cincinnati
9. University of California - Davis
10. University of Iowa

If you have questions or need more detail, write to Joe jgallen@hsph.harvard.edu.

Best wishes,
Amy

Amy Kostant
Science Communication Network (SCN)
O: 301-654-6665
C: 202-255-6665
amy@sciencecom.org
Hi Amy-

I think several of our students would be interested in signing, but I think they need to see the article before signing. I went to the Environmentalist Papers site but couldn't find it. Can you send it or a link to it?

Thanks,

Pat

---

Hi All,

I'm circulating this on behalf of Joe Allen as it may be of interest for you and your students:

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Amy

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Science Communication Network (SCN)
O: 301-654-6665
C: 202-255-6665
amy@sciencecom.org
From: Amy Kostant <amy@sciencecom.org>  
To: "Hunt, Pat" <pathunt@vetmed.wsu.edu>  
Sent: 4/19/2017 11:09:03 AM  
Subject: RE: Environmentalist Papers - student essay for sign on

Im glad you have students who may be interested! I love giving students a voice.
FYI -- I couldnt find it either. Emily had to show me where.

From: Hunt, Pat [mailto:pathunt@vetmed.wsu.edu]  
Sent: Wednesday, April 19, 2017 2:06 PM  
To: Amy Kostant  
Subject: Re: Environmentalist Papers - student essay for sign on

Never mind! I just found it on the link to sign.

From: Amy Kostant <amy@sciencecom.org>  
Date: Wednesday, April 19, 2017 at 9:44 AM  
To: "tc1u@andrew.cmu.edu" <tc1u@andrew.cmu.edu>, "CranmerJoanM@uams.edu" <CranmerJoanM@uams.edu>, "deborah_cory-slechta@urmc.rochester.edu" <deborah_cory-slechta@urmc.rochester.edu>, "pldefur@igc.org" <pldefur@igc.org>, "sgilbert@innd.org" <sgilbert@innd.org>, "tyrone@berkeley.edu" <tyrone@berkeley.edu>, "heilig@sfms.org" <heilig@sfms.org>, "Hunt, Patricia Ann" <pathunt@wsu.edu>, "dickjackson@ucla.edu" <dickjackson@ucla.edu>, "phil.landrigan@mssm.edu" <phil.landrigan@mssm.edu>, "BLanphear@sfu.ca" <BLanphear@sfu.ca>, Pete Myers <jpmyers@ehsic.org>, "porris@uic.edu" <porris@uic.edu>, "dozonoff@bu.edu" <dozonoff@bu.edu>, "gprins@uic.edu" <gprins@uic.edu>, "tschettler@igc.org" <tschettler@igc.org>, "snyderh@email.chop.edu" <snyderh@email.chop.edu>, "shanna.swan@mssm.edu" <shanna.swan@mssm.edu>, Fred Vom Saal <vomsaalF@missouri.edu>, "bernard_weiss@urmc.rochester.edu" <bernard_weiss@urmc.rochester.edu>, "WoodruffT@obgyn.ucsf.edu" <WoodruffT@obgyn.ucsf.edu>, "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, "shuk-mei.ho@uc.edu" <shuk-mei.ho@uc.edu>, "stahlhutr@missouri.edu" <stahlhutr@missouri.edu>, "blumberg@uci.edu" <blumberg@uci.edu>, "svogel@edf.org" <svogel@edf.org>, Laura Vandenberg <lvandenberg@schoolph.umass.edu>, "carl-gustaf.bornehag@kau.se" <carl-gustaf.bornehag@kau.se>, "RHAUSER@hohp.harvard.edu" <RHAUSER@hohp.harvard.edu>, "leonardo.trasande@nyu.edu" <leonardo.trasande@nyu.edu>, "kkreider@unfoundation.org" <kkreider@unfoundation.org>, "itescua@UCMAIL.UC.EDU" <itescua@UCMAIL.UC.EDU>, "michael.antoniou@kcl.ac.uk" <michael.antoniou@kcl.ac.uk>, "sheldon.krimsky@tufts.edu" <sheldon.krimsky@tufts.edu>, "dr.karp@thehappiestbaby.com" <dr.karp@thehappiestbaby.com>, Emily Copeland <emily@sciencecom.org>, Gabriela Silvani Antonelli <gabriela@sciencecom.org>, "jgallen@hsph.harvard.edu" <jgallen@hsph.harvard.edu>, "Andreas.Kortenkamp@brunel.ac.uk" <Andreas.Kortenkamp@brunel.ac.uk>, Chris Portier <cportier@me.com>, "jerryheindel@gmail.com" <jerryheindel@gmail.com>  
Subject: Environmentalist Papers - student essay for sign on

Hi All,
Im circulating this on behalf of Joe Allen as it may be of interest for you and your students:

Three graduate students from the Harvard T.H. Chan School of Public Health have written an article entitled The Future of Environmental Health Is Now" to call our political leaders to action on stronger environmental health protections. This article, from the perspective of the current student generation, is part of The Environmentalist Papers series spearheaded by Dr. Joseph Allen at Harvard. We would like to invite your students to sign their names onto the article using this link.

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9. University of California - Davis
10. University of Iowa

If you have questions or need more detail, write to Joe jgallen@hsph.harvard.edu.

Best wishes,
Amy

Amy Kostant
Science Communication Network (SCN)
O: 301-654-6665
C: 202-255-6665
amy@sciencecom.org
Okay, you are going to force me to come into the 21st century and use the video option. Thanks for persisting!

yes. It handles up to 20

On Jun 19, 2017, at 1:21 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Wow, Pete, I cant believe that you set the meeting up for me. Will this link work for 6 of us????????

Im at a meeting in Flagstaff. Tomorrow at 3 ET works for me. Heres a zoom URL and also a phone number if you dont want video.

Hi Pat Im available both 2 or 3 EST, though 3 would be better. This is particularly shocking since the IRG is supposed to be the scientific review, not Council. Not only that but I doubt anyone is better than Roy at these measurements. This is highly disturbing.
On Jun 19, 2017, at 1:24 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hi Pete and Tom-

I am trying to book a call for 2 or 3pm EST tomorrow and wondering if either of you would be available. Below is a chain of emails that includes one from Thad Schug telling Roy and me that NIEHS decided not to refund our grant (this grant went from triage to 9th percentile). The reasons are nutty, so we forwarded the email to Jerry for advice his reply is there too. Fred has also weighed in and, like Jerry, he is incredulous.

I am convinced that the whole thing is political. I dont know how to fight, but I want to try and I am going to need all the help I can get.

Pat

From: jerry heindel <jerryheindel@gmail.com>
Date: Saturday, June 17, 2017 at 5:53 AM
To: "Gerona, Roy Roberto" <Roy.Gerona@ucsf.edu>
Cc: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: RE: ES013527

Wow, this is unprecedented. This actually means it is likely that NIEHS specifically brought this to the attention of council and asked that they not fund it based on guidance from NTP and FDA. I know Linda too is not supportive of measuring BPA in blood. It is very unusual that NIEHS would override a review. However if we dont/cant measure it in blood how will we ever know the actual BPA level in humans and the amount available for tissue uptake.

It is especially disheartening since you were part of the NIEHS funded study that showed it is possible to measure BPA in blood. As to what to do, I dont really know as I have never seen this situation in my 25 years in the Extramural Division at NIEHS. NEVER! I dont even know who to respond
Dear Jerry,

I hope you're doing well. We would like to seek guidance on how to respond to the decision made regarding our recent grant application to NIEHS. Our proposal received a ninth percentile score. However, based on the deliberation of the NAEHS Advisory Council, our application was not deemed worthy of funding based on concerns regarding the measurements of BPA and its metabolites in blood and tissues we collected for the study (re:contamination). As you were aware during the Round Robin, we have carefully addressed these concerns in our measurements in blood and my laboratory has gone on to transfer our method to urine and other tissues. Publications have been written on our work where we have carefully presented evidence for some of the unseemingly high measurements we obtained. We have also expanded our method to include bisphenol alternatives and our current proposal aims to further include novel alternatives that we will discover through a non-targeted approach. Some of the data that we generated contradicts what were previously published by the CDC, NTP and FDA on BPA but we have...
painstakingly addressed these contradictions before publishing our results and provided proofs that validated our results. We think that instead of bashing our unpopular results, it is worth investigating them further and the proposal that we laid out to accomplish this was highly recommended by the study section. Thus, we think that our proposal was unfairly dismissed by the Council.

We would like to seek your advice on how to go about appealing this decision. Will you be able to spare me and Pat some time Monday or Tuesday on a conference call to discuss this.

Thanks,
Roy

Roy Gerona, Ph.D.
Assistant Professor
Director, Clinical Toxicology and Environmental Biomonitoring Lab
Department of OB/Gyn and Reproductive Sciences
University of California, San Francisco

<33450A60ED034F65811A2478F8BA8332.png>

From: Schug, Thaddeus (NIH/NIEHS) [E] <schugt2@niehs.nih.gov>
Sent: Friday, June 16, 2017 12:09 PM
To: Hunt, Pat
Cc: Gerona, Roy Roberto
Subject: Re: ES013527

Hello Pat and Roy- We recently had our NAEHS advisory Council meeting, plus several other meetings, in which we discussed applications near the funding line.

Unfortunately, based on advisement of the NAEHS Council and other review considerations, we will not be funding your application. The overriding concern in this application dealt with the proposed methods for measuring and interpreting bisphenol and conjugate concentrations. The preliminary data in the proposal show extremely high exposure levels of bioactive bisphenols in urine and blood, and disproportionate levels of metabolites. These levels defy a broad body of recent experimental and computational evidence gathered by NIEHS, NTP, FDA and CDC. There is concern that the irregular levels of bisphenols and metabolites in the samples are a reflection of contamination, which is common in hospital settings and pre- and post- sample collection.

There was also concern that your proposal relies heavily on measuring bisphenols in blood and tissues from retrospective samples. Recent clinical, biomonitoring, and animal studies overwhelmingly conclude that blood and
tissue are not ideal matrices for measuring bisphenols because of the propensity for contamination. Accordingly, FDA, EFSA, and other regulatory agencies simply do not support measuring bisphenols in blood.

Based on these concerns, it was widely agreed upon that accurately correlating maternal and fetal bisphenol exposure levels with ovarian dynamics in the fetus, which is a central scientific aim of the proposal, would not be possible. Similarly, it will not be possible to correlate bisphenol exposure levels with genetic variation and placental metabolism. Because the samples have been collected over a lengthy period, there is no means to retroactively correct for pre- and post-handling contamination.

Please consider discussing with me, or other NIEHS program staff, any future studies involving this topic area prior to submission.

Thad

From: "pathunt@vetmed.wsu.edu" <pathunt@vetmed.wsu.edu>
Date: Wednesday, June 14, 2017 at 2:03 PM
To: Thaddeus Schug <schugt2@niehs.nih.gov>
Subject: ES013527

Hi Thad-

Roy Gerona and I have been anxiously awaiting news on our grant. I know that council met last week. Can you give us any information?

Pat

------------------------
Patricia Hunt
Meyer Distinguished Professor
School of Molecular Biosciences
Washington State University
PO Box 647520
Pullman, WA 99164-7520 (for letters)
Or
1715 NE S Fairway Rd
Room 333, Pullman, WA 99164-7520 (for FedEx)

509-335-4954

<33450A60ED034F65811A2478F8BA8332.png>
Wow, Pete, I can't believe that you set the meeting up for me. Will this link work for 6 of us?????????

From: Pete Myers <jpmyers@ehsic.org>
Date: Monday, June 19, 2017 at 12:41 PM
To: "R. Thomas Zoeller" <tzoeller@bio.umass.edu>
Cc: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: Re: ES013527

I'm at a meeting in Flagstaff. Tomorrow at 3 ET works for me. Here's a zoom URL and also a phone number if you don't want video.

---

On Jun 19, 2017, at 11:15 AM, R. Thomas Zoeller <tzoeller@bio.umass.edu> wrote:

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Tom

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243
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From: jerry heindel <jerryheindel@gmail.com>
Date: Saturday, June 17, 2017 at 5:53 AM
To: "Gerona, Roy Roberto" <Roy.Gerona@ucsf.edu>
Cc: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: RE: ES013527

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Or
1715 NE S Fairway Rd
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509-335-4954

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From: Pete Myers <jpmyers@ehsic.org>
To: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
Sent: 6/20/2017 8:56:09 AM
Subject: Re: ES013527

yes. It handles up to 20

On Jun 19, 2017, at 1:21 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Wow, Pete, I cant believe that you set the meeting up for me. Will this link work for 6 of us????????

From: Pete Myers <jpmyers@ehsic.org>
Date: Monday, June 19, 2017 at 12:41 PM
To: "R. Thomas Zoeller" <tzoeller@bio.umass.edu>
Cc: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: Re: ES013527

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Topic: Tom, Pat, Pete
Time: Jun 20, 2017 3:00 PM Eastern Time (US and Canada)

Join from PC, Mac, Linux, iOS or Android: https://zoom.us/j/41 <paste this URL into your browser

Or iPhone one-tap (US Toll): +14086380968, 41 or +16465588656, 41

Or Telephone:
Dial: +1 408 638 0968 (US Toll) or +1 646 558 8656 (US Toll)
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Amherst, MA 01003
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From: Gerona, Roy Roberto
Sent: Friday, June 16, 2017 6:47 PM
To: jerryheindel@gmail.com
Cc: Hunt, Pat
Subject: Fw: ES013527

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Assistant Professor
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Department of OB/Gyn and Reproductive Sciences
University of California, San Francisco

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From: Schug, Thaddeus (NIH/NIEHS) [E] <schugt2@niehs.nih.gov>
Sent: Friday, June 16, 2017 12:09 PM
To: Hunt, Pat
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Subject: Re: ES01352

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Thad

From: "pathunt@vetmed.wsu.edu" <pathunt@vetmed.wsu.edu>
Date: Wednesday, June 14, 2017 at 2:03 PM
To: Thaddeus Schug <schugt2@niehs.nih.gov>
Subject: ES013527

Hi Thad-

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ph: (413) 545-2088
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http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

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509-335-4954
Hi Amy-

Great to hear from you and also to hear that you are involved in the fan. I've been hoping to get to DC and have a chance to talk with you, but I am no longer on study section so the opportunity just hasn't arisen.

I was not asked to sign the statement on triclosan and triclocarban but would be happy to do so, if it is not too late. I wrote a chapter for Fred's recent book, Integrative Environmental Medicine. I've attached a copy because it profiles parabens, Quats, and triclosan/triclocarban. Sorry that it is kind of a mess its the final proofs and the publishers tried to make quite a lot of changes (we didn't let them get away with it). The book is now published.

With warm regards,

Pat
**Abstract:** Use of emphasis on the antibacterial capability of personal care products and household and commercial cleaners with antibacterial capabilities has increased as a result of the introduction of an increasing array of chemicals into our daily lives. Human exposure to an array of these chemicals occurs through the use and ingestion of products containing them. In addition, because these products are washed down the drain, they are discharged with wastewater into fields, lakes, streams, oceans, and municipal water systems. This chapter focuses on summarizing the uses, persistence, routes of human exposure, and potential health effects of four common environmental chemicals—parabens, triclosan, triclocarban, and quaternary ammonium compounds. We have chosen to focus on these four high-volume production chemicals/chemical classes because exposure to them is ubiquitous, environmental contamination is significant, and evidence of harm has emerged. These chemicals represent only the tip of a large iceberg of man-made environmental contaminants, together they illustrate how the rapid introduction of new chemicals into consumer products must be weighed against the unavoidable environmental contamination and potential biological effects that may ensue.

**Key Words:** Disinfectant, antibacterial, biocide, parabens, triclosan, triclocarban, quaternary ammonium compounds, endocrine-disrupting chemicals.

**Commented [AU1]:** The chapter abstract and words were edited for content and length (maximum 10 key words). Please check them carefully.
TOXIC CONSEQUENCES OF CLEANING CHEMICALS

Patricia A. Hunt, Ph.D., Terry C. Hrubec, D.V.M., Ph.D., and Vanessa E. Melin

Key Concepts

- The addition of antimicrobials to household and personal care products has resulted in intimate daily contact with a wide array of chemicals designed to indiscriminately kill both good and bad microbes.

- The rapid adoption of these chemicals for use in consumer products has resulted in extensive environmental contamination and ubiquitous exposure.

- Because some biocides are endocrine-disrupting chemicals, they can have the potential to induce adverse developmental, reproductive, neurological, and immunological effects in humans and wildlife.

- Parabens are used as preservatives in personal care products, and all widely used forms appear to be physiologically estrogenic. Their widespread use and extensive environmental contamination, however, constitute a serious confounder to assessments of the health effects of this class of chemicals.

- The broad-spectrum antimicrobials triclosan and triclocarban are used in a wide range of cleaning supplies and personal care products. Evidence that
they disturb thyroid homeostasis makes their widespread contamination in wildlife and the environment a concern.

- Quaternary ammonium compounds, or {QACs}, are commercial disinfectants whose efficacy has resulted in their extensive use in consumer applications. Although the toxicity of these compounds has been insufficiently evaluated, heavy use of QACs has produced widespread environmental contamination.

**INTRODUCTION**

Long before germs were linked to disease, cleanliness in operating and hospital environments was key to reducing illness. The concept of clean has evolved into a societal quest for a germ-free environment. Despite our attempts to kill them, the amazing adaptive ability of microorganisms twists our weapons of destruction into an evolutionary accelerant that generates “superbugs” with resistance to the chemicals used against them. To add to our plight, human exposure to the antimicrobial residues in the environment diminishes our natural immunity, impairs reproductive health, and may have other serious human health consequences.

Burgeoning understanding of the human microbiome adds a new dimension to our view of microorganisms. Although the study of the human microbiome is in its infancy, a fascinating and growing body of evidence implicates good bugs in metabolic, nutritional, and immunological homeostasis. Microorganisms likely play a major role in human disease and human health. The recognition that our lives are so intimately intertwined with microbiota that we cannot live happily without them suggests that devising new and better ways of sanitizing our environment is not without peril.
The post-WWII era brought a rapid influx of chemicals into the lives of people living in developed countries, with the United States leading the charge in both production and consumption. The rapid pace of product development was accompanied by improved marketing strategies. This cycle has continued and increased in voracity, and today we are faced with a ceaseless barrage of advertisements for antibacterial soap, germ-killing cleaners, and hand sanitizers on the internet, radio, television, billboards, and even receipt papers. Antibacterial soap, germ-killing cleaners, and hand sanitizers have become commonplace. In the course of our quest for germ-free lives, we have inadvertently welcomed a host of chemicals designed to indiscriminately kill both good and bad microbes into the most intimate aspects of our lives.

APPROACHES TO CONTROLLING MICROORGANISMS:

DEFINING THE APPROACHES

Defining the approaches taken to control, prevent, or destroy microorganisms is an essential first step. Although the general term, "biocide," is used for chemical agents that control microorganisms, an important distinction is made with respect to where they are used and whether they destroy or inhibit growth: Antisepsics are used on living tissue, whereas disinfecting agents are used on inanimate objects. Disinfecting agents are antimicrobial pesticides used to control harmful microorganisms, including bacteria, viruses, and fungi. They are regulated by the U.S. Environmental Protection Agency (EPA) and can be broadly classified as sanitizers, disinfectants, and sterilants.

Sanitizers are designed to reduce but do not completely eliminate microorganisms. Disinfectants are designed to destroy or inactivate most microorganisms.
and some viruses, but they may not eliminate spores. Sterilants are designed to physically or chemically destroy or eliminate all forms of life, including spores.

**Some Biocides That Are Endocrine-Disrupting Chemicals (EDCs)**

The National Institutes of Health (NIH) National Institute of Environmental Health Sciences (NIEHS) defines endocrine-disrupting chemicals (EDCs) as chemicals that may interfere with the body’s endocrine system and produce adverse developmental, reproductive, neurological, and immunological effects in both humans and wildlife. EDCs can be naturally occurring (e.g., phytoestrogens) or man-made chemicals. Man-made EDCs include a diverse range of compounds with many applications, including pesticides, industrial chemicals, pharmaceuticals, and personal care products.

EDCs tend to be stable, which makes them suitable for industrial applications. It can also make them persist in the environment for years, resulting in exposure long after chemical use has been discontinued or banned. The dependence of human physiology and male and female reproduction on carefully orchestrated hormonal cues makes EDCs a threat to of particular concern from the standpoint of human health. Accordingly, in this review of the environmental and biological effects of biocides focuses on - particular attention has been paid to their potential endocrine-disrupting effects.

In this chapter, we review four common classes of biocides—parabens, triclosan, triclocarbon, and quaternary ammonium compounds (QACs)—because adverse health effects have been ascribed to them and because their prevalence in household and personal care products makes them ubiquitous environmental contaminants. The properties, uses, and potential environmental and
biological effects are summarized for each. These biocides illustrate the potential hazards of the 21st century approach to controlling microorganisms in daily life.

**PARABENS**

**Uses and What are They and what are their Endocrine-Disrupting Properties**

Parabens are synthetic alkyl esters of $p$-hydroxybenzoic acid that were first used as preservatives in pharmaceuticals in the mid-1920s, but rapidly expanded for use in a wide range of consumer products. (reviewed in 40).

The most commonly used parabens are methylparaben, ethylparaben, n-propylparaben, n-butylparaben, isobutylparaben, isopropylparaben, and benzylparaben. The most common metabolite of these parabens is $p$-arabhydroxybenzoic acid (PHBA), which can be conjugated to $p$-hydroxyhippuric acid (PHHA). Parabens are effective against Gram-positive bacteria, yeast, and molds, but they have little effect on bacterial spores and no effect on viruses, mycobacteria, or prions.

Like many EDCs, endocrine-disrupting chemicals, the potential effects of parabens have been dismissed by many on the grounds that their low affinity for the classical estrogen receptors makes them only weakly estrogenic and unlikely to induce biological effects. However, data from the in vitro estrogen receptor assay and the in vivo uterotrophic assay suggest that all widely used parabens are physiologically estrogenic. Other mechanisms of action consistent with an endocrine-disrupting role have been reported, including binding to the androgen, thyroid hormone, and peroxisome proliferator-activated-$\gamma$-gamma (PPAR$\gamma$) receptors; inhibition of the sulfotransferase enzyme; and mitochondrial toxicity (8,21,87 and reviewed in 8).
**Routes of Where are They and How are We Exposed?**

Due to their low cost, high water solubility, and stability, parabens are used as preservatives in a wide range of cosmetics and personal care products such as shampoos, and facial and skin cleansers and lotions. Methylparaben and n-propylparaben are the most common parabens in consumer products, and they are often used together. Amounts of less than 0.3% are typical in these products, although mixtures of parabens of up to 0.8% are allowed. Parabens are also used as antimicrobials in some processed foods, in food packaging, as preservatives in pharmaceuticals (http://www.cdc.gov/BIOMONITORING/Parabens_BiomonitoringSummary.html), and in industrial products such as varnishes, glue, and animal feed (reviewed in 40).

Exposure is thought to occur orally from the consumption of food and pharmaceuticals and transdermally from the use of paraben-containing products on the skin. However, parabens have also been detected in air, dust, and soil, and biomonitoring data are consistent with widespread exposure. In analyses of 2,548 urine samples collected from the general population of the United States in 2005 and 2006 as part of the annual National Health and Nutrition Examination Survey (NHANES), methylparaben, methy and n-propylparaben were detected in more than 90% of samples, and ethylparaben and butylparaben in more than 40%. Levels were higher in adolescent and adult women than in men, and these variations in levels were ascribed to differences in the use of personal care products. Similarly, a screen of Danish men found methylparaben and n-propylparabens in urine from 98% of subjects and also in most serum samples.
Since the publication of these initial studies, data from studies too numerous to cite have reported widespread exposure in different populations of children and adults around the world. In addition to underscoring the pervasiveness of exposure, the combined data from these studies provide evidence that exposure is related to lifestyle. Paraben levels in men and women have been correlated with their use of personal care products.\(^6,9\) and reviewed in \(^6\). Importantly, a three-day intervention study involving Latina girls, not only provides compelling evidence that exposure is influenced by consumer choices and, but documents reductions in exposure levels within days of discontinuing paraben-containing products.\(^{41}\) (see Chapter 14).

**How Persistent are They in the Environment?**

Parabens are thought to be rapidly metabolized and eliminated from the body, and, as detailed, biomonitoring suggests that parabens are detectable in the urine of nearly almost everyone in developed countries. They are a significant water contaminant due to discharge from factories producing parabens and urban wastewater that contains residue from consumer products. Wastewater treatment is effective in removing parabens, but effluent from treatment facilities releases them into the environment.

Parabens are readily biodegradable under aerobic conditions, but they remain stable over time in anaerobic sludge.\(^{40}\) Parabens also are highly reactive with chlorine, raising concern that chlorination of wastewater effluent produces halogenated parabens that may be especially persistent contaminants.\(^{40}\) A study of marine mammals in U.S. coastal waters provided sobering evidence of a high prevalence of parabens.
(predominantly methylparaben) in eight species of marine mammals, and astonishingly high levels in some individuals.\textsuperscript{96}

**What are the Current Health Concerns?**

Most attention has focused on two health concerns: effects on reproductive health and breast cancer.

**Male Reproductive Effects.** Epidemiological data on the effects of parabens on male reproduction are limited to two studies from infertility clinics. An association between the levels of butylparaben and DNA damage in sperm was reported in male partners attending an infertility clinic.\textsuperscript{60} A subsequent study focused on in vitro fertilization (IVF) outcomes, and, although based on a very small sample size, it found a slight decrease in the odds of live birth associated with paternal urinary levels of methylparaben and propylparaben.\textsuperscript{27}

As has been seen for other extensively studied EDCs (e.g., BPA, reviewed in),\textsuperscript{73} experimental findings with respect to the effects of parabens on male reproductive health have varied. This in part reflects, at least in part, differences in the species and strains of animals used, the timing, duration, and route of exposure, and the end points evaluated.

**The Importantly,** doses in most studies were designed to correspond to the acceptable daily intake dose of 10 mg/kg/day. Although, no effect on male rodents exposed during fetal development has been reported in several studies,\textsuperscript{24,49,86} others have reported reduced sperm counts or testosterone levels in association with either exposure during both prenatal and early postnatal development or postnatal exposure alone to butylparaben,\textsuperscript{49,68,101} or n-propylparaben.\textsuperscript{69} One study examined the
effect of butylparaben on spermatogenesis in the rat and found a significant increase in spermatogenic cell apoptosis several hours after the administration of a single dose.\textsuperscript{3} Thus, based on the available data, there is substantial evidence that exposure during early postnatal development can adversely impact male reproductive health, but data on the effects of prenatal exposure are insufficient.

**Female Reproductive Effects.** Epidemiologic data on female reproductive health are extremely limited and confined to studies of infertility patients. An initial study reported an inverse association between urinary levels of propylparaben and diminished ovarian reserve.\textsuperscript{83} A subsequent analysis by the same group, however, found no association between urinary paraben levels and IVF outcome for women undergoing infertility treatment.\textsuperscript{64}

Experimental data are also limited. The most comprehensive analysis of the effects of prepubertal exposure on sexual maturation in the female rat found morphological changes in the uterus and ovary and, as well as, changes in the timing of sexual maturation and estrus cycle length with high doses of methylparaben and isopropylparaben.\textsuperscript{90} Studies of exposure during fetal development are limited.\textsuperscript{2} No effects were reported in an industry study,\textsuperscript{24} but altered gene expression in the ovary and decreased leptin levels have been reported in female rat fetuses exposed to butylparaben.

**Breast Cancer.** The clinical use of diethylstilbestrol (DES) in the 1940s through— the 1970s to treat high-risk pregnancies has provided compelling evidence that developmental exposure to synthetic estrogens increases the risk of breast cancer in
and concern that environmental exposure to EDCs may be affecting the incidence of female cancers is growing (reviewed in 77).

Widespread use of parabens in cosmetics and personal care products and reports of detectable levels of parabens in human breast tissue, milk, and tumors raise many concerns. Data directly bearing on the issue, however, are largely confined to in vitro studies, in which parabens have been reported to stimulate the proliferation or alter expression profiles of MCF-7 breast cancer cells (e.g., 13,20,70,74,94). Importantly, the in vitro nature of these studies does not diminish their importance. The inherent difficulty of conducting meaningful epidemiological studies of such pervasive chemicals and, coupled with the lack of a suitable animal model for human breast cancer, makes these essential studies. For example, one recent study demonstrating that epidermal growth factor receptor ligands enhance oncogene expression in butylparaben-primed breast cancer cells illustrates how in vitro models can be used to gain important insight into the mechanism(s) of action in vivo.

Parabens: The Take-home Message

The use of parabens in a wide range of personal care products has made them significant environmental contaminants. Like other EDCs originally categorized as weakly estrogenic, recent data suggest that the endocrine-disrupting properties of these chemicals are likely to be complex. Their pervasiveness makes establishing harmful effects in humans virtually impossible, but, importantly, recent data suggest that savvy consumers can significantly reduce their exposure by avoiding personal care products containing parabens.

TRICLOSAN
Triclosan is an antimicrobial agent that has been used for more than 40 years as a disinfectant and preservative. It is incorporated in medical and household cleaning products and in personal care products. Triclosan is also incorporated in plastics, fabrics, toys, paints, medical devices, and kitchen utensils that are designed such that they leach the chemical for extended periods of time.

Triclosan, or 5-chloro-2-(2,4-dichlorophenoxy)-phenol, is classified as a halogenated aromatic hydrocarbon and is structurally similar to polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and dioxin. Production estimates from 2007 found yearly global production to be more than 1500 tons, with more than 300 tons produced in the United States and more than 450 tons produced in Europe. In Europe, about 85% of the total volume of triclosan is used in personal care products, 5% in textiles, and 10% in plastics and food contact materials.

As an antimicrobial, triclosan is active against most Gram-negative and Gram-positive bacteria, and some fungi. It is bacteriostatic (i.e., stops bacteria from reproducing) at low concentrations and bactericidal (i.e., kills bacteria) at higher concentrations. At sublethal concentrations, it acts by inhibiting bacterial lipid biosynthesis. At bactericidal concentrations, it permeates the bacterial cell wall and targets multiple cytoplasmic and membrane sites, including RNA synthesis and the production of macromolecules. In addition to bacteria, triclosan is toxic to many other organisms in the ecosystem, including aquatic plants, invertebrates, fish, frogs, and mammals. Triclosan has low acute toxicity and for a long time was considered safe.
but however, there is increasing evidence that triclosan alters the endocrine and reproductive systems, and interferes with neural and immune function.

Triclosan has both thyroid hormone and gonadotropin hormone activity (reviewed by 93), and is structurally similar to thyroid hormone. Thyroid hormones play a pivotal role in regulating adult metabolism, and during development, they are essential for cell differentiation and neural development. Environmentally relevant concentrations (i.e., relevant to human exposures) of triclosan have been reported to alter the thyroid hormones T3 and T4 in both male and female rats, and exposure is thought to induce hepatic enzymes involved in T4 metabolism, thereby reducing circulating levels. In frogs, triclosan has been reported to interfere with thyroid hormone-mediated limb development and decrease expression of thyroid receptor mRNA. In vitro studies of rat and human cells suggest that triclosan affects a number of different biochemical processes important for thyroid hormone homeostasis (reviewed by 18). If triclosan also perturbs the thyroid axis in humans, the implications for developmental processes could be profound.

The effect of triclosan on gonadotropin hormones is less clear. It is structurally similar to known estrogenic and androgenic EDCs, including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and bisphenol A. Triclosan can bind both estrogen and androgen receptors and can exert estrogenic, weak androgenic, and anti-androgenic effects (reviewed by 93). It also acts as an anti-androgen by inhibiting testosterone production at a number of steps in the synthetic pathway. The available evidence suggests that triclosan acts at multiple steps in the pathways for both estrogen and androgen signaling.
Adverse effects have been reported in several species and in cell lines, and the combined data suggest that the biological effects of triclosan exposure likely depend upon the tissue, developmental stage, and level of exposure. Importantly, triclosan that enters the body is metabolized, and the impact of these metabolites is likely to be species-specific but has not been studied in detail.

Routes of Where is It and How are We Exposed?

Triclosan is contained in a wide range of personal care products, including toothpaste, deodorant, shampoo, soaps, and detergents, and cosmetics. In 2010, use in personal care products and cosmetics was estimated to account for 99% of triclosan use. It is also incorporated into manufactured goods, including medical devices, children’s toys, carpets, kitchen utensils, and food storage containers, and an increasing number of clothes and fabrics are treated with triclosan to reduce odors and impart antibacterial properties to the material.

Human exposure is commonplace, and triclosan residues can be measured in human blood, urine, tissue, and breast milk. Triclosan is detected in 75% of urine samples and 97% of breast milk samples in the United States and Sweden. Human exposure occurs through oral ingestion (e.g., toothpaste, mouthwashes, and dental treatments), and infants can be exposed through breast milk. Triclosan in personal care products can also be absorbed through the skin. In humans, the primary route of excretion is in the urine, and urinary concentrations are a good measure of exposure.

How Persistent is It in the Environment?
An estimated 95% of the triclosan in consumer products is washed off the skin and ends up in residential wastewater. Removal of triclosan through wastewater treatment is highly variable, ranging from no removal to 100%. Incomplete removal results in the release of triclosan into rivers, streams, and lakes, but an estimated 50% of triclosan in wastewater will partition into and remain in biosolid sludge. Through the spreading of sludge onto soil, triclosan contaminates soils and surface waters. Triclosan is widely detectable in surface waters and wastewater effluent in the United States, Canada, Europe, Australia, Japan, and China, and is one of the top 10 most frequently encountered contaminants in U.S. rivers and streams.

Triclosan is lipophilic, moderately water soluble, and relatively persistent in the environment, with a half-life of at least 11 days in river water. In aerobic soils, biodegradation occurs with a half-life of 18 days, but under anaerobic conditions (i.e., sediment and sewage sludge), triclosan can persist for years. In fact, Triclosan and its breakdown products have been measured in 30-year-old sediment from Lake Greifensee in Switzerland and in 40-year-old sediments from both fresh and estuarine water in the United States.

In personal care products, concentrations are typically in the range of 0.1% to 0.3%. After wastewater treatment, concentrations can reach 0.01 to 2.7 µg/L in effluent and 5 to 55 mg/kg in sewage sludge (i.e., biosolids). In surface water, triclosan concentrations up to 2.3 µg/L have been reported, with 0.8 mg/kg found in freshwater and estuarine sediments.

Although these environmental levels may seem low compared to the concentrations used in consumer products, they have profound effects on the ecosystem.
For example, triclosan in biosolids applied to soils can alter nitrogen cycling and inhibit plant growth, and levels in surface water are sufficient to disrupt development in amphibians and fish.\textsuperscript{19}

In addition to direct toxic effects on organisms in the ecosystem, the formation of toxic by-products in the environment is a concern. Triclosan breaks down into lipophilic, stable, and bioaccumulative persistent compounds—most notably dioxins and chloroform—that may be more toxic than triclosan itself.\textsuperscript{19}

Chloroform forms through the reaction of triclosan with chlorine or chloramine added during wastewater processing and also in drinking water treatment. Although environmental concentrations of triclosan react with chlorine to form chloroform during purification of drinking water, the amount formed is low and unlikely to pose a health risk. However, significant amounts of chloroform are formed when treated drinking water is combined with triclosan-containing products, such as when washing dishes or showering.\textsuperscript{19} Chronic exposure to chloroform can cause liver damage and possibly cancer.\textsuperscript{59} Additionally, 2,4-dichlorophenol (2,4-DCP) and 2,4,6-trichlorophenol (2,4,6-TCP) are produced by the degradation of triclosan, and the U.S. EPA has flagged both as priority pollutants due to their higher stability, well-known toxicity, and endocrine-disrupting activity.\textsuperscript{19}

**What are the Current Health Concerns?**

The potential health issues of triclosan include endocrine disruption, altered immune and skeletal muscle function, antibiotic resistance, and the formation of carcinogenic byproducts. (reviewed in \textsuperscript{19}) Additionally, while not a direct health concern,
triclosan alters many components of the ecosystem, endangering its ecosystem stability and, indirectly, threatening human health.

The known health effects caused by triclosan include disruption of both thyroid hormone homeostasis and gonadotropic hormones, as discussed above. While these effects are significant, recent evidence also suggests effects on other organ systems as well. Using data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES), urinary triclosan levels were compared with serum cytomegalovirus (CMV) antibody levels and diagnosis of allergies or hay fever in adults and children older than 6 years of age in the United States. Triclosan levels were positively associated with allergy and hay fever, suggesting that triclosan exposure could affect immune function and be associated with other inflammatory diseases.

A subsequent epidemiologic study based on NHANES data found a positive association between urinary triclosan concentration and increased body mass index (BMI), strengthening support for an effect of triclosan on immune function.

Experimentally, triclosan has been reported to alter contractility in both skeletal and cardiac muscle, reducing grip strength in mice and swimming ability in fish, and it has been identified as a hepatic tumor promoter in mice.

Triclosan: The Take-Home Message

Triclosan is a serious environmental contaminant. It is pervasive and stable in the environment, has endocrine-disrupting ability, is toxic to plants and aquatic organisms, is degraded to toxic by-products, and has potential for creating antimicrobial resistance. The increased use of triclosan in personal care products stems from relaxed regulation.
combined with aggressive and widespread advertising that reinforces fears of microbial infection.

Although soaps containing less than 1% are no more efficacious than non-antimicrobial soap, concentrations in hand and dish soaps marketed as “antibacterial” are typically 0.3%. In 2005, an FDA panel determined that there was a lack of data demonstrating evidence of the benefits of triclosan use. One concern is that serious damage to the environment and potential harm to human health is occurring through the use of a chemical that provides little or no obvious benefit.

**TRICLOCARBAN**

**Uses and What is It and What are Its Endocrine-Disrupting Properties?**

Triclocarban, or N-(4-chlorophenyl)-N-(3,4-dichlorophenyl)urea, is a nonphenolic carbanilide with use and properties similar to those of triclosan. Triclocarban is also a broad-spectrum antimicrobial and is added to a wide range of medical products, household cleaning supplies, and personal care products at levels of 0.5% to 5% by weight. It is not a “new” chemical; triclocarban was originally introduced as a surgical scrub, but it has been used in personal care products such as hand soaps, detergents, creams, and toothpaste, and detergents since the late 1950s (reviewed in). By comparison with triclosan, however, triclocarban has received considerably less attention. This does not reflect the fact that it is inherently less interesting or of less concern, only that it could not be analyzed by gas chromatography and mass
spectroscopy (GC-MS) and had to await the development of liquid chromatography and mass spectroscopy (LC-MS) analytical tools.

The potential endocrine-disrupting abilities of triclocarban have not been studied in detail. Data from in vitro nuclear receptor bioassays, however, suggest that triclocarban may possess unusual endocrine-disrupting ability. Specifically, although triclocarban alone exhibits little or no agonist activity, it appears to amplify the response of both androgen and estrogen receptors to steroid hormones. Triclocarban also is a potent inhibitor of the human soluble epoxide hydrolase enzyme.

**Routes of Where is It and How are We Exposed?**

Like triclosan, human exposure to triclocarban occurs through a wide variety of personal care products and other consumer goods, with oral ingestion and transdermal absorption thought to be the primary routes of human exposure. Based on urinary levels, showering with triclocarban-containing soap has been suggested to result in absorption of approximately 0.6% of the triclocarban contained in the product.

Biomonitoring studies have been few and limited in scope. Triclocarban, however, has been detected in human urine and cord blood in the United States, with the latest study reporting detectable levels in 87% of urine samples from pregnant women tested at a hospital in Brooklyn, NY. Exposure levels have varied greatly in small biomonitoring studies conducted around the world, likely reflecting differences in the analytical methods employed. However, in a recent biomonitoring study of a Chinese population, the frequency of triclocarban detection exceeded that of triclosan (99% and 69%, respectively) in adult urine samples.
How Persistent is It in the Environment?

Triclocarban is an important environmental contaminant and, together with triclosan, is considered among the most frequent organic wastewater contaminants.\textsuperscript{16} Triclocarban, however, may be even more environmentally persistent. A recent study of different environmental compartments calculated half-lives for triclocarban ranging from 0.75 days in air to 540 days in sediment.\textsuperscript{38} Further, triclocarban levels exceeded those of triclosan both in an analysis of bioaccumulation in algae from a stream receiving wastewater from a treatment plant receiving stream in Texas\textsuperscript{16}, and in samples from urban streams in Baltimore, MD.\textsuperscript{38}

Like triclosan, triclocarban is enriched in biosolids and persists under anaerobic conditions. An evaluation of their removal by conventional sludge processing systems reported more rapid removal of triclosan, consistent with the idea that triclocarban is less readily biotransformed.\textsuperscript{66} Similarly, in a recent study using carrot cell cultures, triclocarban proved more resistant to metabolism by plants than triclosan.\textsuperscript{95}

What are the Current Health Concerns?

As for triclosan, experimental evidence suggests that triclocarban exposure may induce disturbances in thyroid homeostasis. Fewer studies have evaluated the effects of triclocarban, but two in vitro studies using rat cells provide evidence of exposure effects.\textsuperscript{44} Altered expression of thyroid hormone responsive genes was observed in pituitary cells exposed to triclocarban,\textsuperscript{44} and a slightly stronger inhibition of iodide uptake than triclosan was reported in thyroid cells.\textsuperscript{95} Importantly, the lowest triclocarban concentration eliciting an effect in iodide uptake studies is thought to be within
the range of human exposure levels. The limited data available suggest that both broad-spectrum antimicrobials have the potential to disrupt thyroid homeostasis.

**Triclocarban: The Take-Home Message**

Like triclosan, the use of triclocarban as an antimicrobial is widespread, but its value in personal care products is questionable, especially in light of the high level of environmental contamination caused by this use. Compared with triclosan, triclocarban has been less well studied. Nevertheless, detectable levels in human biospecimens, and widespread contamination in wildlife and the environment have been found is evident. At the same time, Evidence that both triclosan and triclocarban have endocrine-disrupting properties is accumulating, and the need for studies to assess their biological activities is urgent.

**QUATERNARY AMMONIUM COMPOUNDS (QACs)**

**Uses and What are They and What are Their EDC-Endocrine-Disrupting Properties?**

Quaternary ammonium compounds, or QACs, are cationic disinfectants with antimicrobial, surfactant, and antistatic properties. QACs have been in use for approximately 70 years and serve a variety of applications. In the United States, they are registered as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and many number of QAC formulations are listed on the federal registry as microbiocides and algaecides.

QACs are effective against most bacteria, fungi, protozoa, and some viruses. The bactericidal effects of QACs are mediated through the adsorption of the cationic molecule
to negatively charged proteins on bacterial cell membranes. Their antibacterial value, however, is limited by their lack of sporicidal action and their ineffectiveness against Clostridium difficile and some Ggram-negative bacteria. Nevertheless, QACs have rapidly replaced traditional oxidizing disinfectants such as sodium hypochlorite and hydrogen peroxide because they do not decolorize fabric, are non-corrosive, and leave no odor.

QACs consist of a central nitrogen atom surrounded by four functional groups that influence the antimicrobial, surfactant, and anti-static activity of the molecule. Modifications to QAC functional groups for improved stability, solubility, and product application have generated four chemically diverse groups of QACs. The earliest (i.e., group I QACs) contain long-chain alkyl (C8 to C18) functional groups and have antimicrobial activity. Group II QACs possess non-halogenated benzyl functional groups and have detergent and biocidal capacity. Group III QACs have dichlorobenzyl and trichlorobenzyl substitutions for enhancement of biocidal activity, and while group IV QACs have unusual substituents and are use in textiles, laundry products, and as well as in cosmetics.

The most common QACs in commercial cleaning and disinfectant solutions are alkyl dimethyl benzyl ammonium chloride (ADBAC) and didecyl dimethyl ammonium chloride (DDAC). Each compound contains a mix of alkyl chain lengths: C12 to C18 for ADBAC and C8 to C16 for DDAC.

Because oral or inhalation exposure to QACs is considered moderately toxic and dermal exposure slightly irritating, therefore, appropriate personal protective equipment is recommended during the application of QACs. At present, little is known about the
endocrine-disrupting potential of QACs. A recent report, however, suggests that ADBAC (i.e., benzalkonium chloride [or BAC]) disrupts cholesterol biosynthesis and, because cholesterol serves as a substrate for all steroid hormones, this raises the possibility that QACs are EDCs. This finding, coupled with the growing evidence of biological effects, indicates that further studies of the mechanisms of action of these compounds are urgently needed.

**Routes of Where are They and How are We Exposed?**

Standards set by the U.S. Occupational Safety and Health Administration (OSHA) to mitigate occupational exposure to blood-borne pathogens have resulted in listing by the U.S. Environmental Protection Agency (EPA) of several QAC formulations as effective against common clinical pathogens. As a result, QACs are common in clinical environments and commercial settings. The efficacy of QACs over a broad range of temperatures and pH levels has led to extensive incorporation of these compounds in consumer applications, including algaecides in swimming pools, antiseptics in candy lozenges, and preservatives in eye drop solutions.

In 2002, QACs were reported to be the most common disinfectant in food production, storage, and preparation facilities in the United Kingdom, and their global use in large-scale agricultural and food processing operations contributes to the prevalence of QACs in commercially prepared food. The extensive use of ADBAC and DDAC QACs in industrial, commercial, and residential settings suggests that humans are chronically exposed. Although little is known about dermal exposure,
occupational exposure to ADBAC through inhalation is common among janitorial and health care workers.\textsuperscript{10,65,75}.

**How Persistent are They in the Environment?**

Because QACs are used as dilute solutions, the contamination potential of these compounds has largely been ignored. ADBAC-containing disinfectant solutions that do not exceed 400 ppm are not considered significant sources of human exposure and are exempt from food residue tolerance requirements in the United States.\textsuperscript{30} Extensive commercial use of QACs, however, has led to significant environmental contamination and there is evidence that these chemicals persist in the environment for many months after their use is discontinued.\textsuperscript{61}

In addition to being a wastewater contaminant, QACs are used during municipal wastewater treatment to reduce the coliform load. It is not surprising that analysis of urban sewage runoff suggests that QACs are more prevalent than other aquatic contaminants, including chlorinated pesticides, polychlorinated biphenyls, and polyaromatic hydrocarbons.\textsuperscript{56} The propensity for cationic QAC molecules to adsorb sludge, and the fact that they undergo little to no biodegradation under anaerobic conditions, makes them environmentally persistent.\textsuperscript{33} Consequently, QACs have been proposed as useful tools for the evaluation of sewage contamination in aquatic environments.\textsuperscript{57} Despite the fact that QAC contamination in aquatic environments is ecologically significant, studies of the toxic effects of these compounds on aquatic organisms are limited.\textsuperscript{35}

**What are the Current Health Concerns?**
Experimental studies in rats provide evidence that oral exposure to high concentrations of QACs can be lethal, and death following ingestion of a 10% BAC solution has been reported for elderly humans. There is some evidence that QACs may be genotoxic, with genetic damage reported in human peripheral lymphocytes from healthy volunteers.

Reports of occupational asthma in healthcare workers using ADBAC-containing disinfectants suggest that exposure may cause respiratory and mucosal irritation. Sensitization and irritation of skin and mucous membranes have been reported following occupational and residential use of BAC concentrations as low as 0.1% to 0.5%. Experimental studies in mice also provide evidence that QAC inhalation results in pulmonary irritation and inflammation, and in vitro studies of mouse lung fibroblasts implicate DDAC in pro-inflammatory effects leading to pulmonary fibrosis and disrupted transforming growth factor-β signaling.

ADBAC and DDAC have also been identified as reproductive toxicants in the mouse; the chemicals decreasing sperm counts in males and ovulation rate and offspring number in females. Experimental studies of toxicity in other tissues, however, have been limited to in vitro toxicity studies of ADBAC and DDAC using corneal, epithelial, and pulmonary cell lines. ADBAC is a common preservative in eye drop solutions, and corneal and conjunctival cytotoxicity has been reported at the low concentrations typically present in ophthalmic preparations (0.01% to 0.02%). Spermicidal formulations containing BAC are available outside of the United States, and studies of human vaginal epithelial cell lines suggest that these products may induce mucosal toxicity through the induction of inflammatory interleukin release.
Although relatively few studies of the biological effects of QACs have been undertaken, collectively, data from in vivo and in vitro studies suggest that ADBAC and DDAC are cytotoxic. In the absence of corroborating data from epidemiologic studies, however, the risk posed to humans (other than for occupational asthma) remains unclear. ADBAC and DDAC are increasingly combined in commercially available products, but few studies have evaluated the toxicity of QAC mixtures.

**QACs: The Take Home Message**

QACs are considered an important class of disinfectants whose toxicity has been insufficiently evaluated. The prevalence of QACs as disinfectants in occupational settings, as antimicrobials in personal care products, and as common environmental contaminants, makes the degree of human exposure significant. While the lack of research attention devoted to evaluating the potential health effects of these compounds is surprising, the limited data available data raise serious concerns about the potential adverse effects of exposure on the lung and reproductive health of adults and as well as effects on the developing fetus.

Because the optimization of QAC moieties for product-specific functions likely influences their ability to exert biologic effects, assessment of different QAC groups is essential. QAC mixtures are commonly used, and, since QACs may act synergistically to produce greater toxic effects, assessment of common mixtures is essential to evaluate chemical risk. Given these concerns, identifying the sources and understanding the extent of human exposure and understanding the potential health effects of QACs are critical tasks.

**SUMMARY AND FUTURE DIRECTIONS**
In this chapter, we have focused on existing evidence of health and ecological effects of four persistent and widespread environmental contaminants. All four have been implicated in reproductive effects, and while triclosan and triclocarbon also appear to interfere with thyroid homeostasis. Further, there is concern that their antimicrobial properties and combined with widespread use, have led to increased bacterial resistance to these biocides. Lastly, all four chemicals contaminate much of the ecosystem, where they impact many plant and animal species, and the long-term consequences of ecosystem exposures are not yet unknown. Importantly, parabens, triclosan, triclocarbon, and QACs represent a tiny subset of the chemicals that enter daily life from the air, food, water, prescription drugs, personal care products, manufactured products, and cleaners used in homes and public spaces, and this select group of biocidal chemicals illustrates several critical concepts.

Chemicals originally designed for clinical and commercial purposes are now being used in a wide variety of consumer products. This is clearly illustrated by triclosan and triclocarbon, which proved efficacious in the clinical and industrial realm and were rapidly adapted for use in personal care and other consumer products. This transition occurred in the absence of sufficient safety testing, and also without sufficient evidence that these chemicals are, in fact, efficacious in consumer products.

As the number of chemicals in everyday use has expanded, the sense of caution and concern about their use has waned. As illustrated by the parabens and QACs, quaternary ammonium compounds, the ability to rapidly engineer man-made compounds to modify or magnify desirable attributes can result in an ever-evolving class of chemicals with different properties. The expanding and evolving array of related
chemicals, however, impedes efforts to understand biologic[al] and environmental effects, since because each chemical variant has will have slightly different properties. Further, because their transition occurs in the absence of sufficient testing, the recognition that a chemical poses a risk to human health or the environment may not occur until exposure or contamination has become widespread.

*Our chemical finesse is not without cost.* Available evidence suggests that the chemicals reviewed in this chapter have significant potential to harm humans and other species. Their use has become so pervasive that most the majority of the population is exposed. In essence, We have allowed inadequately tested chemicals to enter the most intimate aspects of our lives and are conducting population-wide experiments without controls. Elucidating the impacts of chemical exposure on human health means trying to understand both the effects of individual chemicals and as well as how their effects are influenced by genetic diversity, lifestyle choices, and other pervasive environmental chemicals.

There are other potentially serious consequences of the extensive and indiscriminant use of biocides, such as possible effects on human immunity and an increased propensity of microbiota to develop resistance. These emerging concerns underscore the urgency of reforms, including: 1) testing of chemicals before prior their marketing, 2) devising methods of tracking and controlling the applications of approved chemicals, and 3) developing transparency in the use of approved chemicals that not only provides consumer awareness and, but facilitates the detection of health or environmental effects.
The role of the clinician is **essential**. Given the flaws in current chemical safety and risk assessment procedures, the task before us is **daunting**. It is clear that chemical exposures—especially those that occur during development—**can have the potential to affect** the incidence of chronic non-communicable diseases later in life. Ideally, we need a patient **exposome** (i.e., record of in utero and early-life exposure) to understand how specific developmental exposures affect adult health and disease.

In the meantime, clinicians can **only** work with **their** patients to understand how past or current exposures **may** affect their health. This does not, however, mean that clinicians are **powerless**. By informing patients about growing areas of concern, the medical profession is in a powerful position to affect change. **Concerned** scientists and clinicians can, of course, work with their professional societies to affect change; however, a more effective route is through patient education.

Clinicians’ most important role at present is to rationally and responsibly voice their concerns to the general public. Consumers make daily choices, and, as a recent three-day intervention study involving Latina girls (i.e., HERMOSA study) demonstrated, simple changes in consumer choices can reduce exposure. Citizen concern about the health effects of chemical exposure can drive changes in product formulation and as well as legislation for adequate safety testing of chemicals in consumer products. To feel powerless in the face of information on chemicals **such as** those reviewed in this chapter is to fail to understand the power of the opinions of scientists and clinicians to influence society.

REFERENCES


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| 49. | Kang, K.S., Che, J.H., Ryu, D.Y., Kim, T.W., Li, G.X., & Lee, Y.S. | Decreased sperm number and motile activity on the F1 offspring maternally


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*Toxicology and Industrial Health* 17:31–39.


The study found that oestradiol in MCF7 human breast cancer cells.


release and PPARgamma activation. *Molecular and Cellular Endocrinology*


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proliferation and estradiol secretion in MCF-7 and MCF-10A cells.


This is awesome Pat! Thank you. I am going to dive into the details tomorrow! Margaret at the moment is somewhere between Frankfurt and Tokyo. She'll be away from Switzerland until a week from Sunday. I know she will check in with email but don't know exactly when. We will hear from her!

Fabulous!

p

On Feb 17, 2017, at 3:17 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hi Margaret and Pete,

I've been thinking a lot about the phone call and the herculean task you have taken on. I know that your first goal is to build a network of scientists. To attract scientists, I think it is critical to have a message that is strong and clear (details come later). In thinking about it yesterday after the call, I realized that it is the same message that I have been toying with in my teaching and considering for either a new institute at my current university or as my mission in a new job.

I have attached a set of slides that walk you through it very quickly. The message that will help co-op scientists into the Fan is that science not only needs to grow in depth, but also in BREADTH. Scientists are pragmatic. They will want to know how. The how here is easy and it fits in with Margaret's mycelium analogy: It starts with leadership at a few institutions and new thinking that infiltrates. I've been focusing on the next generation, but I'm no longer sure that we have the luxury of that much time.

As you know, I believe there is great power in simplicity. I would argue that this type of concise messaging is essential for scientists, but also can be easily adapted for other target audiences. The framework is simple, but once you get scientists to buy in, they will be only too happy to flesh out the details for you (likely more details than you ever wanted!).

Let me know what you think of the slides.

Pat

<For Pete and Margaret2.pptx>
Thanks for this.
I'm here early and just realized the Ritz is a bit of a walk and it's HOT—can I pick you up?

Sent from my iPhone

> On Jun 23, 2017, at 12:50 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:
> Amy-
> Here is the final text of the paper. The figures are too big to get through the hotel server!
> Pat
> <Successive Generations of Exposure.docx>
If you are not going to be in the office, it doesn't make sense to go to DuPont. We are at the Ritz (I know, it doesn't sound like NIH, does it?). If you know someplace fun to go for tea or a drink, I would love to simply enjoy an hour or two with you.

I will be able to give you a better idea of when we will finish Friday after tomorrow's session.

I am really looking forward to seeing you, Amy!

Sent from my iPad

> On Jun 21, 2017, at 8:23 PM, Amy Kostant <amy@sciencecom.org> wrote:
> 
> Friday afternoon is perfect. It's the same to me to drive to Dupont as to Tysons. Which is better for you?
> 
> ------Original Message------
> From: Hunt, Pat [mailto:pathunt@vetmed.wsu.edu]
> Sent: Wednesday, June 21, 2017 8:14 PM
> To: Amy Kostant
> Subject: Re: Friday
> 
> Sorry, I wasn't clear - I meant Friday. Thursday evening isn't possible because the meeting will go on until who knows when and then we will just grab dinner and crash. Let me know if Friday works - I will likely be mid afternoon.
> 
> On 6/21/17, 4:17 PM, "Amy Kostant" <amy@sciencecom.org> wrote:
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I arrived in DC this afternoon. Study section should finish around lunchtime. We are at Tyson's Corner. If I head for DuPont Circle after the meeting ends, will you have time to meet?

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Pat

Sent from my iPhone
Hi Pat -
Great about your paper! Can you send it to me? Do you know the pub date? Get together today? I have Friday on my calendar but am wide open tomorrow too. Tonight I have a house full of 15 year old boys....

Sent from my iPhone

> On Jun 21, 2017, at 6:42 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:
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> Hi Amy-
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> Pat
> 
> Sent from my iPhone
Given the source of the rankings, I don't think any trends or comparisons can be justified. Although Gina Kolata's serial errors are consistent with ACSH's ranking.

On Mar 8, 2017, at 10:00 AM, Swan, Shanna <shanna.swan@mssm.edu> wrote:

Surprised to see NY Times ranked so low!

On Mar 8, 2017, at 9:45 AM, Pete Myers <jpmyers@ehsic.org> wrote:

Nature has an editorial about this new ranking by ACSH of science magazines.


They completely miss the point that ACSH is a notorious front group for industry. So many science journalists are politically tone deaf and constantly embarrass themselves.
Hi Amy-

Gail told me about the paper but did not send a copy to me, so thanks for providing that and the press release and journalist letter. The timing works out and I am pleased to be able to do this for Gail.

I have been out of town for pretty much all of July but am now home and staying put through August. We have taken two short vacations but still feel like we need a vacation! The first was a week in Bend, OR at the end of May where we saw lots of snow and rain. The second was a few days in Strasbourg (Terry was there for a meeting and we thought we would add on a couple days of fun) where the temperature was 100 degrees every day but one. I hope you have better luck! The Cape is lovely this time of year, so I hope your vacation proves restful, relaxing, and fun.

I think of you often and would love the chance to catch up. I finished with study section in June (our last meeting was on the west coast), so I will no longer be making regular trips to Washington, but I will get there and you are at the top of my list when I do!

With warm regards,

Pat

---

Dear Pat,

I hope you're well and enjoying summer. I'm headed for vacation on Friday a week in Wellfleet on Cape Cod. Should be lovely were bringing my daughter's boyfriend for entertainment for both kids. Seems a 21-year-old boy has as much fun with a 13-year-old boy as he does with his 19-year-old GF.

Gail said you'd agreed to be an expert who would talk with a reporter or two who may ask for a comment from someone other than an author. Thank you. Gail may have already sent you the paper, but in case not I've attached the paper, our note to journalists, and a press release from the university. I don't think you'll be deluged one or two requests at most, but you know how helpful this is when we do get such a request.

Our note to journalists goes out Monday morning, and I'll be away so Emily will send you a note if she gives any reporters your contact info (email only).

Do you have plans to come east anytime soon? It's been way too long!
Please email them, Emily. I've had a few more emails from Linda and she is not feeling well. She is opting out of a conference next week and I think it is very generous of her to agree to talk to reporters in view of everything that is going on.

Wonderful news - I can email their press office at UCSF or we can have Linda loop them in...

On Jul 31, 2014, at 2:47 PM, "Hunt, Pat" <pathunt@vetmed.wsu.edu> wrote:

Dear Pat,

Good to hear from you. These are clearly important findings! I have been under the weather and am not sure that I will make the trip to the GRC as planned on August 8th (proposed travel day). If not, then I can be on standby to talk with the press then and on the 11th and 12th. This usually goes through our public relations office at the university. Shall loop them in.

Hope you are well! My best to you and Terry (your Terry, I.e.).

Linda

I hope this finds you happy and well. I am writing in the hope that I can convince you to talk to a few reporters in the middle of August, should the need arise. When I moved to WSU, we had breeding problems that we traced
to the use of a disinfectant containing quaternary ammonium compounds (QACs). We experienced poor pregnancy rates, late fetal demise, birth defects, and low weaning weights. We could not run a controlled experiment because we kept contaminating the environment and, since there was no meiotic phenotype, I didn’t pursue it. I did, however, talk about it at SSR and a Nature reporter who was at the meeting ended up writing a Q and A piece on it (attached). This has led to some interesting calls from dog breeders over the years all reporting the same thing: a very poor breeding season and birth defects or stillbirth. A couple years ago I got a call from Terry Hrubec at VA Tech. She studies neural tube defects and saw an increase in defects in control animals when QACs were introduced in her facility. The first paper will be published in the middle of August and reports increased time to first pregnancy, a decrease in live born pups, and an increase in deaths of mothers at the time of delivery (we know that this is due to late fetal demise but, sadly, she didn’t follow this up in her study).

To make a long story short, we are hoping that this paper gets some media attention. QAC-containing disinfectants are a mainstay in hospitals and other commercial settings and have even made their way into consumer products (including baby wipes!). Terry cannot tackle the human question and, to be honest, I am hoping to get some of my colleagues interested in pursuing human studies. Both Terry and I will talk to reporters, but I think it would also be nice to have a fertility doc who could speak to the larger issue of environmental exposures and human reproduction.

If you are willing and able, I would be happy to talk to you further. I have attached a copy of the manuscript (I don’t have the final proof version yet). It looks like the publication date will be August 13th, which means that reporters would be trying to make contact on the 8th, 11th and 12th.
I have a labradoodle! However, I've been thinking that I would like a small poodle for my next dog. They are great for people with allergies although at times it is hard to have a dog that often seems more intelligent than his people.

Bear witness? I feel like I am living in a cartoon! The next couple years are going to be busy and important ones for us. So glad I have you, Pete, et al.!

First just making sure you know I have two mini-poodles. They're the greatest dogs in the world for small-ish people with allergies. Sounds like a fantastic class! I'm so glad this was helpful. And yeah were considering that at the very least we can bear witness over the next 4 years.

All best,
Amy

Amy, you are the best! Thank you. This will be really great for the class discussion. Last year was very interesting because we started the session talking about how everything is a GMO (I used a poodle as an example of how man has been genetically modifying for decades) and all the students agreed that GMOs are completely safe. The course is only 5 weeks long and we spent most of the time talking about ways of making genetic modifications. The last week we returned to GMOs and I walked them through a bunch of different stories (the papaya, the flavor-saver tomato, etc), reports of adverse effects and how they have been discredited. I also went through the labeling issue and showed them the figures for the California proposition so they could see how much industry is investing. The last class was a mock congressional hearing. To my surprise, I had no trouble getting students to sign on for both the pro and con side and they did a great job of developing compelling arguments. I tried not to introduce any bias, just to talk about how we assess risk, the lack of safeguards to detect effects, etc. It was a blast. I want to do something a bit different this year. The National Academy statement will figure in as will these papers. Thanks for your help.

Great to see the Republicans off to such a strong and positive start today, huh?

With thanks,

Pat
Hi Pat,

Very nice to hear from you! So far, so good here too for the new year. No snow, but lots of people still in a saddened daze over the election. Kind of nice, though, that Pence moved into the neighborhood next to ours, and there are many, MANY, rainbow flags hanging out windows and lawn signs saying, This neighborhood trusts women, in support of Planned Parenthood. Kind of nice that he chose one of the very most progressive communities for his temporary housing.

And yes there are two papers on GMOs both from Michael Antoniou and Robin Mesnage. The first published in December, and the second will publish January 9 both in Scientific Reports (a Nature publication). Both are attached here, but the fatty liver paper is confidential until its published. I'm also attaching Michaels lay summaries for each paper as they may be helpful. In case its of interest, I've also attached Michael and Robins excellent response to critical comments from Science Media Centre. We think (have no proof) that someone from the journal or the university may have leaked the paper to SMC to give them time to get their response ready in advance of publication.

Media coverage of the maize paper was less than it should have been possibly because of the pub date so close to holidays that many journalists were gone, but also possibly because of the SMC comments. Let me know if you need anything more.

All best wishes and I hope to see you in person sometime in the new year,

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---

Hi Amy-

Happy New Year! I hope your year is off to a good start. We have snow, snow, and more snow.

I am writing because Pete mentioned on a recent call that 2 papers on GMO health risks were coming out. I managed to lose my notes so I cant remember the journal or when. I am teaching a course this semester and would like to use them, if possible. I assume that you handled the release and might be able to lead me to the papers.

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With thanks and warm wishes,

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From: Hunt, Pat [mailto:pathunt@vetmed.wsu.edu]
Sent: Monday, January 2, 2017 4:21 PM
To: Amy Kostant
Subject: GMO papers

Hi Amy-

Happy New Year! I hope your year is off to a good start. We have snow, snow, and more snow.

I am writing because Pete mentioned on a recent call that 2 papers on GMO health risks were coming out. I managed to lose my notes so I can’t remember the journal or when. I am teaching a course this semester and would like to use them, if possible. I assume that you handled the release and might be able to lead me to the papers.

I appreciate any help you can provide.

With thanks and warm wishes,

Pat
Bear witness came from new years eve dinner with someone high up in state dept who works on counterterrorism. Shes not at all happy, and said most people at state are staying in their jobs to at least bear witness, and at best stall dangerous change. A lawyer friend at NIH said the same. These are real heroes.
I'm choosing to do lots of yoga, be kind to everyone in my path, and donate to everyone who asks. At least for now. And yes one of my poodles is so smart its scary. He has lots of language and is a leader among neighborhood dogs. The other is 5 years old and still cant remember to pee outside but shes incredibly cute and would go to her death to protect me. I adore them both. (And you've probably already forgotten about that rule the dogs dont sleep in the bed, and if not, you will when you get a small poodle. They're very good sleep buddies.)

I have a labradoodle! However, I've been thinking that I would like a small poodle for my next dog. They are great for people with allergies although at times it is hard to have a dog that often seems more intelligent than his people.

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Pat

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From: Amy Kostant <amy@sciencecom.org>
Date: Tuesday, January 3, 2017 at 4:43 AM
To: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: RE: GMO papers

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Pat
Hi Pat,

Very nice to hear from you! So far, so good here too for the new year. No snow, but lots of people still in a saddened daze over the election. Kind of nice, though, that Pence moved into the neighborhood next to ours, and there are many, MANY, rainbow flags hanging out windows and lawn signs saying, This neighborhood trusts women, in support of Planned Parenthood. Kind of nice that he chose one of the very most progressive communities for his temporary housing.

And yes there are two papers on GMOs both from Michael Antoniou and Robin Mesnage. The first published in December, and the second will publish January 9 both in Scientific Reports (a Nature publication). Both are attached here, but the fatty liver paper is confidential until its published. I'm also attaching Michael's lay summaries for each paper as they may be helpful. In case it's of interest, I've also attached Michael and Robin's excellent response to critical comments from Science Media Centre. We think (have no proof) that someone from the journal or the university may have leaked the paper to SMC to give them time to get their response ready in advance of publication.

Media coverage of the maize paper was less than it should have been possibly because of the pub date so close to holidays that many journalists were gone, but also possibly because of the SMC comments. Let me know if you need anything more.

All best wishes and I hope to see you in person sometime in the new year,

Amy

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Hi Amy -

Happy New Year! I hope your year is off to a good start. We have snow, snow, and more snow.

I am writing because Pete mentioned on a recent call that 2 papers on GMO health risks were coming out. I managed to lose my notes so I can't remember the journal or when. I am teaching a course this semester and would like to use them, if possible. I assume that you handled the release and might be able to lead me to the papers.

I appreciate any help you can provide.

With thanks and warm wishes,

Pat
An integrated multi-omics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process

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Glyphosate tolerant genetically modified (GM) maize NK603 was assessed as ‘substantially equivalent’ to its isogenic counterpart by a nutrient composition analysis in order to be granted market approval. We have applied contemporary in depth molecular profiling methods of NK603 maize kernels (sprayed or unsprayed with Roundup) and the isogenic corn to reassess its substantial equivalence status. Proteome profiles of the maize kernels revealed alterations in the levels of enzymes of glycolysis and TCA cycle pathways, which were reflective of an imbalance in energy metabolism. Changes in proteins and metabolites of glutathione metabolism were indicative of increased oxidative stress. The most pronounced metabolome differences between NK603 and its isogenic counterpart consisted of an increase in polyamines including N-acetyl-cadaverine (2.9-fold), N-acetylputrescine (1.8-fold), putrescine (2.7-fold) and cadaverine (28-fold), which depending on context can be either protective or a cause of toxicity. Our molecular profiling results show that NK603 and its isogenic control are not substantially equivalent.

The application of genetic engineering (GE) to modify edible crops is often advocated as one of the most important scientific advances to improve farming systems and feed the world in a more sustainable manner1. GE has been used to create crops adapted to abiotic stress, resistant to pathogens, with a longer shelf life, or with enhanced nutritional properties. However, commercialization of these traits is currently minor. Agricultural genetically modified (GM) crops are dominated by plants engineered to tolerate application of a herbicide or/and to produce their own insecticides2. A total of 180 million hectares of GM crops are currently cultivated worldwide on around 1.5 billion hectares constituting approximately 10% of global arable land3. Approximately 80% of GM crops have been modified to tolerate application of and thus accumulate glyphosate-based herbicide residues without dying in order to facilitate weed management.

Regulations for the release of genetically modified organisms (GMOs) of any kind in a country are covered by the national biosafety regulations of that nation. Guidance on risk assessment (RA) aim at identifying and avoiding adverse effects by early detection and proper evaluation of intended and potential unintended changes in a GMO. These should be detected and identified at early stages of RA, often referred to as ”hazard identification”. Hazard identification is essential to the RA process as it sets the foundation of what is considered or observed in later steps in the risk assessment process4. In the US, the Food and Drug Administration considers

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GM technology as an extension of conventional breeding and GMO crops are deregulated once nutritional and compositional “substantial equivalence” is demonstrated. The set of parameters and analyses necessary to declare a GMO as substantially equivalent to its conventional counterpart is still vague and focuses on a restricted set of compositional variables, such as the amounts of protein, carbohydrate, vitamins and minerals. GMOs are then declared substantially equivalent when sufficient similarities appear for those selected variables. Remarkably, while a majority of GMO crops have been modified to withstand and thus accumulate a herbicide without dying, analysis for residues for such pesticides are neglected in compositional assessment.

Recent technologies used to ascertain the molecular compositional profile of a system, such as transcriptomics, proteomics, metabolomics, epigenomics and mirnomics, collectively referred to as “omics technologies”, are used extensively in basic and applied science. Comparative omics analyses have been performed comparing GMO crops and their isogenic counterpart. A number of them have shown metabolic disturbances from potential unintended effects of the GM transformation process in Bt maize, glyphosate-tolerant soybean, potato, cotton and rice. However, these studies do not report consistent or coherent results, which can be explained by the use of a variety of genetic backgrounds and/or different growth conditions, as well as variations in the technologies and threshold levels applied. Indeed, the majority of authors of these types of studies conclude that the statistically significant changes observed between the conventional and the GM varieties are not biologically significant because they fall into the range of variations obtained in the comparisons between different conventionally-bred varieties, and under different environmental conditions. However, other authors conclude that observed differences could reflect biologically significant, GM transformation process induced changes in protein profiles or metabolism when appropriate near-isogenic controls were applied and test crops grown at the same time and location to avoid differences brought about by variable environmental conditions. Currently, no regulatory authority requires mandatory untargeted molecular profiling omics analysis to be performed but some acknowledge their potential relevance for food and feed derived from GM plants with specific metabolic pathways modified, or in situations where a suitable comparator is not available.

Despite being declared to be ‘substantially equivalent’, off target effects have been observed in non-target species for Bt toxin-producing GMO crops. Additionally, laboratory animal feeding trials performed with some GM plants in comparison to the non-GM counterpart have been proposed to provide evidence of ill-health effects. Several laboratory studies consisting of 90-day feeding trials in rodents have been conducted to evaluate the safety of GMO crop consumption. These investigations have frequently resulted in statistically significant differences in parameters reflective of disturbances in various organ systems and in particular liver and kidney biochemistry, but with interpretation of their biological significance, especially with respect to health implications, being controversial. Such differences in outcome in such laboratory animal feeding studies could have multiple sources including the presence of GMO-associated pesticide residues.

In an effort to provide insight into the substantial equivalence classification of a Roundup tolerant NK603 GM maize, we have performed proteomics and metabolomics analyses of NK603 (sprayed or unsprayed with Roundup) and isogenic maize kernels (Fig. 1). We used a TMT10plex™ isobaric mass tag labelling method and quantified proteins by Liquid chromatography-tandem mass spectrometry (LC-MS/MS). The metabolome profile was determined by ultrahigh performance liquid chromatography-tandem mass spectroscopy (UPLC-MS/MS). Altogether, our integrative analysis shows that the GM transformation process used to generate NK603 maize caused deep alterations in the proteome and metabolome profiles of this crop and results in marked metabolic changes. We conclude that NK603 maize is not compositionally equivalent to its non-GM isogenic counterpart as previously claimed.

Results
The objective of this investigation was to obtain a deeper understanding of the biology of the NK603 GM maize by molecular profiling (proteomics and metabolomics) in order to gain insight into its substantial equivalence classification. We began by undertaking an unsupervised exploratory analysis of variance structure. We integrated metabolome and proteome profiles of the NK603, cultivated either with or without Roundup, and its isogenic counterpart, into a two-step multiple co-inertia analysis (MCIA) process. First, a one-table ordination method transforms each multidimensional dataset (hyperspaces) separately into comparable lower dimensional spaces by finding axes maximizing the sum of the variances of the variables. The resulting variance structure can be described by a PCA (Additional file 3). The results show a clear separation of each feed type (NK603, NK603+ Roundup and control) in both platforms. Control samples had the most distinct proteome and metabolome profiles as observed in PCA plots.

In a second step, the variance structures analyses from metabolome and proteome profiles were combined into a single analysis (Fig. 2). This aims to find new axes on which the two hyperspaces are projected by maximizing the square covariance. Figure 2A shows the projection of metabolome and proteome profiles onto the first two principal components of MCIA. Absolute eigenvalues of these components are given by a bar plot (Fig. 2B). The transgenic feed samples NK603 and NK603+ Roundup are separated from the non-transgenic control (Isogenic) along the first component (horizontal axis). This clustering accounts for most of the variation (percentage of explained variance of 56.7%). The NK603 maize sprayed with Roundup separates from the unsprayed NK603 maize on the second component (vertical axis, percentage of explained variance of 16.6%). The lines connecting the different dots are proportional to the divergence between the different variables of the dataset. A relatively high correlation is depicted by the short edges. It shows similar trends in metabolome and proteome profiles, and also between the two cultivations, indicating that the most variant sources of biological information were similar. The projection of individual protein or metabolites on a 2-dimensional space (Fig. 2C) showed a mix pattern indicating that no particular subsets of variables are driving the clustering of groups. Finally, Fig. 2D shows the pseudo-eigenvalues space. The proteome samples (blue and green dots) are highly weighted on the horizontal axis indicating that this dataset is the highest contributor of the clustering of the transgenic feed samples from the
control. By contrast, the differences between the NK603 maize sprayed with Roundup and the unsprayed NK603 maize are mostly due to the composition of the metabolome since the latest has a high weight on the vertical axis (red and black dots) of the pseudo-eigenvalues space. The fold changes observed in the comparisons of the NK603 maize sprayed with Roundup, the unsprayed NK603 maize and the isogenic control corn were highly correlated between the two cultivations performed during two different growing seasons (Additional file 4). Overall, the MCIA shows that the GM transformation process was the major contributor to variation in the protein and metabolite profiles rather than environmental factors such as the spraying of a pesticide or the growing season.

We next conducted a statistical evaluation of the biological differences resulting from the GM transformation process, as well as from the spraying of Roundup, by pairwise comparisons in order to identify proteins and metabolites associated with possible metabolic alterations. The list of proteins and metabolites having their levels significantly disturbed is given in Additional files 5 and 6, respectively. Figure 3 shows the statistical significance of differential protein/metabolite levels by volcano plots along with respective fold changes. While only one protein is newly produced as a result of the transgene insertion, a total of 117 proteins and 91 metabolites have been altered in maize by the genetic transformation process and insertion of the EPSPS-CP4 cassette (Isogenic vs NK603 panel, Fig. 3). One protein (B4G0K5) and 31 metabolites had their expression significantly altered by the spraying of the Roundup pesticide (NK603 vs NK603 + Roundup (R) panel, Fig. 3).

The NK603 maize has been engineered to express a modified version of the Agrobacterium tumefaciens strain EPSPS-CP4\(^2\). Two peptides (IAGGEDVADLR and gLGNASGAAVATHLDHR) from EPSPS-CP4\(^2\) were detected and quantified by undertaking a specific targeted data analysis (Fig. 4). Their location on EPSPS-CP4 is shown by Fig. 4C. Reporter ion intensities for EPSPS-CP4 peptides in the NK603 + Roundup and the NK603

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**Figure 1. Flowchart of the experimental procedure.** Harvested grains from NK603 GM maize cultivations, sprayed (NK603 + R) or not (NK603) with Roundup, were compared to their nearest isogenic non-transgenic control (Isogenic) grown under similar normal conditions. Two biological replicates were obtained by performing two cultivations at the same location in different years. Maize grains were analyzed by different mass spectrometry methods to determine proteome and metabolome profiles in 3 technical replicates.
were on average respectively 7 and 10 times higher than in the isogenic control. The observed signal for the non-transgenic corn probably represents non-specific background noise since it does not contain the EPSPS-CP4 gene. This would be caused by the co-isolation of other peptides in the corresponding MS/MS experiment, which gives rise to low intensity reporter ions in the control channels.

We analysed the biological information contained in proteome profiles from the NK603 and its isogenic counterpart to see if they bear a signature representative of metabolic disturbances caused by the insertion of the transgene cassette and/or the expression of bacterial EPSPS-CP4. Among different pathway enrichment analysis software tested, String was chosen due to its in-house predictions and homology transfers, as well as its connection to many fine external database resources, and thus its ability to identify a larger number of proteins. Nevertheless, our interpretation remained limited by the quality of protein annotation in such databases. A total of 42.7% (50/117) and 35% (55/156) of the proteins respectively disturbed in the comparison to the unsprayed or the sprayed NK603 maize were uncharacterized or not annotated in the databases (Additional file 5).

Pathway enrichment analysis of differentially expressed proteins in NK603 and NK603 + Roundup feed samples was mainly assigned to carbohydrate and energy metabolism (Table 1). Most of the proteins, including enzymes, associated with these pathways were overexpressed in GM samples (Additional file 5). An increased expression of some proteins involved in glycolysis (FDR adjusted p-value = 4.2e-7), and in particular in the synthesis of pyruvate from D-glyceraldehyde 3-phosphate can be indicative of an increased demand for energy. Among them, pyruvate kinase (B4F9G8), enolase (ENO1), and three glyceraldehyde-3-phosphate dehydrogenases (GAPC1, GAPC2, GAPC3) had their levels increased in NK603 maize. Interestingly, gene ontology terms related to metabolic responses to stress were enriched (FDR adjusted p-value = 1.5e-6) and some heat shock proteins (e.g., HSP82) have been overexpressed.

The comparison between Roundup-sprayed NK603 and control samples revealed a similar pattern to that observed in unsprayed samples. However, glutathione metabolism (KEGG ID 480) showed a significant alteration in sprayed NK603. The proteins assigned to that pathway, glutathione S-transferase 1 and 6-phosphogluconate...
Dehydrogenase (P12653 and B4FSV6 respectively) were more abundant in sprayed samples while another glutathione transferase isoform GST-5 (A0A0B4J3E6) was less abundant. Additionally, the 1-Cys peroxiredoxin PER and the peroxidase were overexpressed. Although only one protein was statistically significantly altered in a pairwise comparison between NK603 + Roundup and NK603 as the effect of Roundup herbicide spray alone, the protein B4G0K5 that has an identified conserved domain of Ricin-type β-trefoil lectin. The Ricin-type β-trefoil is a carbohydrate-binding domain found in a variety of molecules serving diverse functions such as enzymatic activity, inhibitory toxicity and signal transduction34.

The composition of the metabolome is shown in Additional file 6. The most pronounced differences between the NK603 GM maize and its isogenic counterpart mostly consisted of an increase in the amounts of numerous polyamines. The levels of N-acetyl-cadaverine (2.9-fold), N-acetylputrescine (1.8-fold), putrescine (2.7-fold) and cadaverine (28-fold) were increased in NK603. The metabolome profile also highlighted an impairment of energy metabolism. While metabolites from the first part of the TCA cycle had their levels increased (α-ketoglutarate by 1.65-fold and citrate by 1.49-fold), metabolites from the second part of the TCA cycle had their levels decreased (malate by 0.59-fold, fumarate by 0.60-fold, succinate by 0.80-fold). Additionally, while proteins associated with glycolysis were overexpressed, carbohydrate metabolism is depleted in several metabolites (glucuronate by 0.63-fold, glucose 1-phosphate by 0.56-fold, maltolhexaose by 0.28-fold, maltopentaose by 0.51-fold).

Differences due to the pesticide spray were subtle: phenylpropanoid such as 4-hydroxycinnamate (0.63-fold), ferulate (0.59-fold) and sinapate (2.9-fold) were significantly changed. While alterations of the shikimate pathway were not detected, intermediates from aromatic amino acid metabolism (PEP derived) had their level increased (phenyllactate by 1.60-fold, phenylpyruvate by 2.71-fold, N-acetyltetraline by 2.24-fold and xanthurene by 1.52-fold). These changes could be indicative of an increase in amino acid catabolism. However, of note is that PEP itself was not detected in the analysis.

Table 2 provides pathway enrichment analysis of metabolites that were found to be statistically significantly altered in the pairwise comparisons. For the metabolome pathways analysis, the profile of NK603 and NK603 + R showed a distinct pattern compared to the profiles observed in the proteome analysis. From the 10 most altered pathways, these two samples shared only five altered pathways and these suggest an alteration due to the GM transformation process. These pathways revealed an alteration in aspartate, pyruvate and phenylalanine amino acid downstream processes. The NK603 metabolome profile seems to differ from sprayed samples by fatty acid
related pathways and choline, nicotinate and nicotinamide metabolism while sprayed samples showed alterations in serine metabolism and other sugar related metabolism.

The STITCH tool was used to provide a visualisation of predicted interactions of chemicals and proteins that might have a link to the transgene-associated EPSPS-CP4 pathway. The interaction network reveals that some proteins or metabolites altered in the NK603 maize are interacting with EPSPS (Fig. 5). The network formed by these proteins/metabolites is centred on some TCA cycle intermediates, among them, the α-ketoglutarate. One should note that EPSPS is using an energy metabolism intermediate (phosphenolpyruvate) as substrate. Overall, our data shows that the expression of a heterologous EPSPS in the NK603 maize is causing a deep alteration in the proteome and metabolome profiles of feed samples and thus resulting in a metabolic imbalance.

Discussion

In this report we present the first multi-omics analysis of GM NK603 maize compared to a near isogenic non-GM counterpart. Based on analysis conducted by the developer Monsanto Company, NK603 maize was scored as ‘substantially equivalent’ to its isogenic control, which was a major contributor to this product being granted market approval for animal and human consumption in the European Union, United States, Brazil and several other nations. Although NK603 had comparable nutritional and compositional profiles when originally accessed by the developer company upon registration of their product, our analysis at a detailed, in-depth molecular profiling level shows that NK603 grains, with or without Roundup spraying during cultivation, are not equivalent to isogenic non-transgenic control samples (Fig. 2).

The concept of substantial equivalence has long being used in safety testing of GMO crops, but the term and the concept has no clear definition. In 1993 the Organization for Economic Co-operation and Development (OECD) stated that the “concept of substantial equivalence embodies the idea that existing organisms used as food, or as a source of food, can be used as the basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new.” The vagueness of this term generates conflict among stakeholders to determine which compositional differences are sufficient to declare a GMO as non-substantially equivalent. However, the Codex Alimentarius Commission makes it clear that a safety assessment of a new food based on the concept of substantial equivalence “does not imply absolute safety of the new product; rather, it focuses on assessing the safety of any identified differences so that the safety of the new product can be considered relative to its conventional counterpart.” Thus, the concept of substantial equivalence should not be used as a proof of safety. However, it could be used as a first tier in risk assessment to detect any unintended effects of the GM transformation process. Unintended effects can be understood as the effects that go beyond the primary expected
effects of the genetic modification, and represent statistically significant differences in the GMO compared with an appropriate control. Unintended effects during transgenesis include rearrangements, insertion, or deletions during the genetic transformation or during the tissue culture stages of GMO development. A comprehensive characterization of the GM plant at the molecular level could facilitate identification of unintended effects in GMO crops and could be used as a complementary analytical tool to existing safety assessment procedures.

Table 1. Pathway enrichment analysis in proteome profiles of the maize samples. Among different analytical software, String was chosen as it recognized a maximum number of proteins. The maize genome was used as a background list to calculate the p-values of each term. The 10 most enriched GO biological process terms and KEGG pathways (ranked by p-values) are presented. N, number of protein disturbed in each pathway; p-adj, fdr adjusted p-value.
In general, our study design further highlights the importance of restricting comparison to the GMO crop and non-GMO isogenic comparator and cultivation of the two at the same location and season when the objective is to evaluate the effect of the GM transformation process. This is obligatory in order to reduce effects on plant metabolism arising from differing environmental conditions, which can make it difficult to attribute differences that are observed to the procedure of transgenesis. However, even though our experimental design takes into account the effect of the growing season, further experiments made under different environmental conditions would be needed to determine the full range of effects of the GM transformation process on NK603 phenotype. Indeed, virtually all traits are influenced by genotype–environment interactions. Neither genetic differences nor environmental variations alone can account for the production of a particular phenotypic variation. For example, a study of the expression of the transgene encoding a Bt toxin in the MON810 GM maize under different environmental conditions has shown that the phenotype resulting from the GM transformation process is influenced by stressful environmental conditions.

The increasing literature reporting application of omics methods to assess proteome, metabolome and transcriptome profiles in GMO crops shows strong evidence of distinct grain proteomes in other GM maize events, such as MON810 Bt insecticide producing maize. Although the majority of studies have focused on insect-resistant maize (e.g., MON810 event) and most likely because this was the first GM maize to enter the food and feed market, there has also been one previous metabolomics study investigating NK603. Metabolite profiling of NK603 maize kernels were analyzed and approximately 3% of the metabolites detected showed statistically significant differences compared to the respective isogenic lines. Two metabolites (γ-tocopherol and myo-inositol) were found to be significantly different between the two genotypes.

### Table 2. Pathway enrichment analysis in metabolome profiles of the maize samples.

The 10 most altered pathways (ranked by p-values) are presented. The number of metabolites disturbed in each pathway (n) is compared to the total number of metabolites measured for the given pathway (N). Enrichment scores (ES) for each pathway are calculated as follow: ES = (number of significant metabolites in pathway/total number of detected metabolites in pathway)/(total number of significant metabolites/total number of detected metabolites). The p-values were calculated according to a one sided Fisher exact test.

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were less abundant in NK603. Interestingly, γ-tocotrienol and myo-inositol levels were also found to be significantly reduced in our study, and thus attributable to the genetic transformation. This suggests that some metabolic alterations are consistently reported despite a strong background triggered by environmental influence. In a study of two common MON810/non-GM variety pairs subjected to two farming practices (conventional and low-nitrogen fertilization), it was found that up to 37.4% of the variation was dependent upon the variety, 31.9% were the result of the fertilization treatment, and 9.7% was attributable to the GM character.

Alterations can also be found in other plant tissues. For example, analysis of leaves of Brazilian varieties of MON810 Bt maize revealed a total of 32 differentially expressed proteins between GM and non-GM samples that were identified and assigned to carbohydrate and energy metabolism, genetic information processing and stress response.

Our study revealed significant metabolome profile differences between NK603 that was either sprayed or not with Roundup during cultivation (Fig. 2). This was surprising since the single application of this herbicide was prior to development of the maize cobs. In addition, we did not detect glyphosate or AMPA residues in the test maize kernel samples (Additional File 1). This indicates that metabolic differences provoked by an early application of Roundup persisted throughout the life of the maize even in the absence of herbicide residues. At present we can only speculate as to the mechanisms that may explain these effects but they may have their basis in epigenetic programming of gene expression patterns with consequent longer term effects. The spraying of Roundup could have acted as a signal causing an alteration in gene expression patterns in the growing maize. A recent study that demonstrated marked epigenetic (DNA methylation) changes in Arabidopsis in response to treatment with carbendazim supports this possibility. In addition, it has been demonstrated that epigenetic (DNA methylation and post-translational histone modification) patterns acquired in one cultivation can be transgenerationally inherited in an Arabidopsis model system. However, further research would be needed to determine if epigenetic alterations provoked by pesticide exposure can hamper plant phenotypes across generations.

The maize kernels analysed in this study were previously used to feed laboratory animals that formed part of a chronic (2 year) study looking at potential toxic effects arising from the consumption of this NK603 Roundup-tolerant GM maize. A dry feed was formulated to contain 11%, 22%, or 33% of NK603 maize, cultivated either with or without Roundup application, or 33% of the near isogenic variety. Sprague Dawley rats fed
for two years on these diets presented blood/urine biochemical changes indicative of an increased incidence of liver and kidney structure and functional pathology in the NK603-containing diet groups compared to non-GM controls\textsuperscript{35}. Standard biochemical compositional analysis revealed no particular differences between the different maize types tested\textsuperscript{35}. Metabolic disturbances observed in our study may help to understand the negative health effects suggested after the chronic consumption of this GM maize. Alterations in concentrations of metabolites in grains might be directly related to pathogenic effects due to some active compounds that are known to be toxic\textsuperscript{32}. For instance, a soybean glycoprotein allergen (Gly m Bd 28 K fragment) was also found overexpressed in a proteomic study of Roundup Ready GM soybean seeds (MSOY 7575 RR event)\textsuperscript{13}. In our study, cadaverin levels were significantly increased (Log2FC 4.81 for NK603 and 5.31 for NK603+Roundup). Cadaverin plays important roles in lysine biosynthesis\textsuperscript{33} and also glutathione metabolism\textsuperscript{34}. Other similar biogenic amines, such as N-acetyl-cadaverine, N-acetylputrescine and putrescine were also found to be present at higher levels in NK603 in our investigation. Different polyamines have been reported to have different effects, which depend on various factors such as age, tissue or disease status\textsuperscript{55}. In certain contexts some of these polyamines have been found to be protective whereas in other situations they can be a cause of toxicity. On the one hand, toxicological effects such as nausea, headaches, rashes and changes in blood pressure are provoked by the consumption of foods with high concentrations of polyamines\textsuperscript{56}. Putrescine and cadaverine have been reported as potentiators of the effects of histamine, and both have been implicated in the formation of carcinogenic nitrosamines with nitrite in meat products\textsuperscript{37}. On the other hand, certain polyamines can also have beneficial anti-inflammatory effects and have been found to be beneficial during aging in some rodent model systems\textsuperscript{38}. Noticeably, these polyamines were not measured in the first compositional analysis of NK603 maize performed for regulatory purposes\textsuperscript{32}. Overall, whether the increased levels of cadaverine and putrescine found in the NK603 maize samples can account for the signs of potential negative health effects upon its consumption has, as implied by the blood/urine biochemical analysis\textsuperscript{13}, needs to be further analyzed in experiments using more quantitative methods.

Our results suggest that expression of the EPSPS-CP4 transgene alters the oxidative environment in cells, and the increased levels of antioxidant enzymes are likely to be a response to oxidative burst by reactive oxygen species (ROS) in order to maintain proper physiological function. Glutathione metabolism was significantly altered in the NK603 when Roundup was sprayed during cultivation. Glutathione is known to be an important antioxidant in most living organisms, preventing damage to important cellular components caused by several environmental pollutants, including agrochemicals\textsuperscript{39}. Plant glutathione S-transferases (GSTs) are also widely known for their role in herbicide detoxification\textsuperscript{40}. Enzymes involved in combating reactive oxygen species, ascorbate peroxidase, glutathione reductase, and catalase are expressed at a higher level in transgenic soybean seeds\textsuperscript{41}. Levels of ROS and other free radicals in GM food and feed would have to be monitored and quantified by further experiments in order to conclude on their potential impact on the agronomic performances of the plant. Additionally, it is known that polyamines are typically elevated in plants under abiotic stress conditions\textsuperscript{41}. Typically, when cellular polyamine content increases, the levels of hydrogen peroxide also increases, activating antioxidant systems. Unintended effects of the inserted EPSPS-CP4 transgene was linked to energy metabolism disturbances in other studies\textsuperscript{13–15}. It can be hypothesized that the plant is searching for a new equilibrium to maintain heterologous EPSPS-CP4 metabolism within levels that can be tolerated by the plant.

Glyphosate, the active ingredient of Roundup herbicide, inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is the sixth enzyme of the shikimate pathway, and plays an essential role in the biosynthesis of aromatic amino acids and other aromatic compounds in plants\textsuperscript{42}. The EPSPS has a binding site for phosphoenolpyruvate (PEP) and it could be hypothesized that an overexpression of a heterologous EPSPS could provoke a metabolic imbalance by altering the metabolism of PEP. Alterations in intermediate metabolism are corroborated in our experiment by the fact that the network formed by altered proteins/metabolites is centred on some TCA cycle intermediates (Fig. 5) such as α-ketoglutarate. In fact, it is also known that EPSPS inhibition by glyphosate impairs carbon metabolism, in particular by inducing alternative respiration and aerobic fermentation\textsuperscript{43}. In this latest study, the metabolic switch was explained by an accumulation of pyruvate. Thus, if EPSPS inhibition is able to alter intermediate metabolism, a comparable change in the opposite direction could be expected as a result of EPSPS overexpression.

This study is the first and most detailed multi-omics characterization of a widely commercialized GMO crop and its isogenic counterpart. In conclusion, our integrative statistical and bioinformatics analysis allowed us to suggest a mechanistic link between the proteome and metabolome alterations observed and the insertion of a particular transgene. The transformation process and the resulting expression of a transgenic protein cause a general disturbance in the GM plant and it is clear that NK603 maize is markedly different from its non-GM isogenic line at the proteome and metabolome levels. In addition, our data correlates with previous studies, which observed higher amounts of ROS that act as free-radicals promoting oxidative stress in those transgenic plant materials. We also confirm a metabolic imbalance in energy and carbohydrate metabolism. Although a clear mechanistic link between alterations in the GM feed and the possible health effects following long-term consumption of this product remains to be established, the evidence we present clearly shows that NK603 and non-GM isogenic maize are not substantially equivalent and the nutritional quality of GM feed might be hampered by metabolic imbalances related to plant energy and stress metabolism.

Materials and Method

Maize cultivation. The varieties of maize used in this study were DKC 2678 Roundup-tolerant NK603 (Monsanto Corp., USA), and its nearest isogenic non-transgenic control DKC 2675. These two types of maize were grown under similar normal conditions, in the same location and season, spaced at a sufficient distance to avoid cross-contamination. The site of cultivation consisted of an imperfectly drained field with a coarse loam surface texture and fine loam subsoil. A typical soil compositional analysis is provided in Additional File 1. The maize cultivation rows were spaced 75 cm apart, with approximately 30 cm between planted seeds (78,000 seeds/ha).
One pass of the seeder included 4 rows of corn. To avoid edge effects in the field, 2 passes (8 rows) of DKC 2575 (isogenic) were planted as a buffer zone. DKC 2678 (NK603) and DKC 2575 (isogenic) were planted ~ 85 m apart. Half of the DKC 2678 received the treatment with Roundup WeatherMax.

Fertilization was performed with 26 T/ha liquid dairy manure, 100 kg/ha of 30-0-10 fertilizer was broadcast at planting, and 150 kg/ha of 18-46-0 fertilizer banded with the seed. The corn was harvested when the moisture content was less than 30%. All corn varieties were hand harvested by collecting ears in large tote bags to avoid cross contamination. The corn pickers were instructed to pick every ear of corn so as to avoid any risk of quality differentiation. Each corn variety was shelled (kernels removed from the cob) using a small threshing machine designed for this purpose. Each variety was dried in separate bulk drying bins to avoid any risk of cross contamination. The corn was dried at a low temperature (<30 °C) to avoid drying too rapidly and affecting feed quality. The corn was dried to <14% moisture before bagging.

The genetic nature, as well as the purity of the NK603 maize seeds and harvested material, was confirmed by quantitative PCR analysis of DNA samples. One field of NK603 was sprayed once with Roundup at 3 L ha⁻¹ (WeatherMAX, 540 g/L of glyphosate, EPA Reg. 524–537) whilst another field of NK603 was not treated with Roundup. Test samples were produced by two cultivation cycles performed over two growing seasons. All maize samples were analysed for a total of 423 pesticide residues by SGS Institut Fresenius GmbH (Berlin, Germany), including glyphosate and its metabolite AMPA. No pesticide contaminants were detected in any of the samples (Additional file 2). All samples were maintained at ~80 °C until processing for analysis. A schematic overview of our experimental design, sampling strategy and analytical approach is provided in Fig. 1.

**Proteome analysis.** Sample preparation. Ground maize kernel samples were lysed in 8M lysis buffer (urea, NaCl, Tri-HCl, phosphatase and protease inhibitor) and their protein concentration calculated using a Nanodrop protein assay. Samples in triplicate were run through an SDS-PAGE 4–20% polyacrylamide gradient gel at 150 V. Excised gel bands were reduced with dithiothreitol (Sigma-Aldrich Ltd, Gillingham, Dorset, UK), alkylated with Iodoacetamide (Sigma-Aldrich Ltd) and digested with bovine sequencing grade trypsin (Roche, Penzberg, Germany; ref. 11418475001) at 37 °C for 18 hours. Subsequently extracted peptides were labelled with 60 mM TMT10plex Isobaric Label Reagents (ThermoFisher Scientific, Waltham, MA, USA; ref 90406) and the respective samples combined. Labelled peptides were then purified and extracted using Waters Sep-Pak Vac 3cc 200 mg tC18 cartridges, before being separated into 10 fractions by strong cation exchange (SCX) across an increasing salt concentration. The eluted peptide fractions were purified and extracted once again before being lyophilised for direct analysis by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Liquid chromatography-tandem mass spectrometry. Fractionated samples were resuspended in 100 μl of 50 mM ammonium bicarbonate and 10 μl of each of the 10 fractions was loaded onto a 50 cm EASY-spray column (ThermoFisher Scientific). Quantitative analysis was performed using the Orbitrap Velos-Pro mass spectrometer (ThermoFisher Scientific) in positive ion mode. The peptides were separated by gradient elution, from 5–80% 0.1% trifluoroacetic acid in acetonitrile (5–40% from 0–100 minutes, 40–80% from 100–110 minutes), at a flow rate of 300 nL/min. Mass spectra (m/z) ranging from 400–1600 Daltons was acquired at a resolution of 60,000 and the 10 most intense ions were subjected to MS/MS by HCD fragmentation with 35% collision energy.

Data processing. Protein identification was performed with Proteome Discoverer 1.4. Raw files were imported and searched against the UniProtKB/Swiss-Prot Database using Sequest for Proteome Discoverer. Raw files for all fractions were merged together in a single file search for each of the two TMT10plex sets. Precursor mass tolerance for the searches was set at 20ppm and fragment mass tolerance at 0.8ppm. The taxonomy selected was *Zea mays* and three enzymatic mis-cleavages were allowed. Dynamic modifications selected on the search were Oxidation/+15.995 Da (M) and Deamidated/+0.984 (N, Q) and static modifications were Carbamidomethyl/+57.021 Da (C), TMT10plex/229.163 Da (K), TMT10plex/229.163 Da (Any N-terminus). Only peptides with TMT reporter ion signal intensities for all ten samples were used for further bioinformatics analysis.

Metabolome analysis. The metabolome analysis was performed by Metabolon Inc. (Durham, NC, USA) as previously described⁵⁴. Ground maize kernel samples were prepared using the automated MicroLab STAR® system from Hamilton Company (Reno, NV, USA). Several recovery standards were added prior to the first step in the extraction process for QC purposes. In order to remove protein, dissociate small molecules bound to protein or trapped in the precipitated protein matrix, and to recover chemically diverse metabolites, proteins were precipitated with methanol under vigorous shaking for 2 min (Glen Mills GenoGrinder 2000) followed by centrifugation. The resulting extract was divided into five fractions: two for analysis by two separate reverse phase (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one for analysis by RP/UPLC-MS/MS with negative ion mode ESI, one for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI, and one sample was reserved for backup. Samples were placed briefly on a TurboVap® (SOTAX Corp, Westborough, MA, USA) to remove the organic solvent. The sample extracts were stored overnight under nitrogen before preparation for analysis.

Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS) for metabolome analysis. All methods utilized a Waters ACQUITY ultra-performance liquid chromatography (Waters Corp, Milford, MA, USA) and a ThermoFisher Scientific Q-Exactive high resolution/accurate mass spectrometer interfaced with a heated electrospray ionization (HESI-II) source and Orbitrap mass analyser operated at 35,000 mass resolution. The sample extract was dried then reconstituted in solvents compatible to each of the four methods. Each reconstitution solvent contained a series of standards at fixed concentrations to ensure injection and chromatographic...
consistency. One aliquot was analyzed using acidic positive ion conditions, chromatographically optimized for more hydrophilic compounds. In this method, the extract was gradient eluted from a C18 column (Waters UPLC BEH C18-2.1 × 100 mm, 1.7 μm) using water and methanol, containing 0.05% perfluoropentanoic acid (PFPA) and 0.1% formic acid (FA). Another aliquot was also analysed using acidic positive ion conditions, however it was chromatographically optimized for more hydrophobic compounds. In this method, the extract was gradient eluted from the same afore mentioned C18 column using methanol, acetonitrile, water, 0.05% PFPA and 0.01% FA and was operated at an overall higher organic content. Another aliquot was analysed using basic negative ion optimized conditions using a separate dedicated C18 column. The basic extracts were gradient eluted from the column using methanol and water, however with 6.5 mM ammonium bicarbonate at pH 8. The fourth aliquot was analysed via negative ionization following elution from a HILIC column (Waters UPLC BEH Amide 2.1 × 150 mm, 1.7 μm) using a gradient consisting of water and acetonitrile with 10 mM ammonium formate, pH 10.8. The MS analysis alternated between MS and data-dependent MSn scans using dynamic exclusion. The scan range varied slightly between methods but covered 70–1000 m/z.

**Metabolome data processing.** A quality control value assessment was undertaken to determine instrument variability by calculating the median relative standard deviation (RSD) for the internal standards that were pre-mixed into each sample prior to injection into the mass spectrometer. This yielded a value of 3% for instrument variability. Overall process variability as determined by calculating the median RSD for all endogenous metabolites (that is, non-instrument standards) present in 100% of the samples gave a value of 7%. Raw data was extracted, peak-identified and QC processed using Metabolon's hardware and software as previously described.

For plotting of results, a Principal Component Analysis (PCA) was first performed. The language and statistical environment R together with the ade4 package method was employed in order to explore the relationship between GM and non-GM varieties. Second, we performed a Multiple Co-Inertia Analysis (MCIA), using the language and statistical environment R together with the omicade4 package, in order to integrate multiple omics datasets where the same tissue have been assayed multiple times (in this case, proteomics and metabolomics).

Pairwise Welch’s t-tests were performed, for both proteomics and metabolomics datasets, for Isogenic vs NK603, Isogenic vs NK603+Roundup and NK603 vs NK603+Roundup comparisons. The resulting p-values were adjusted by the Benjamini-Hochberg multi-test adjustment method for the high number of comparisons. Volcano plots were also constructed in order to visualize the differences in metabolite and protein expression for each of the comparisons. The aforementioned tests and plots were performed using in-house R scripts. Pathway enrichment analysis of the proteomics dataset was conducted using the web tool STRING v10.0. For the metabolomics data, due to a lack of well-annotated metabolome databases for maize, the pathway enrichment analysis was conducted as follows. First, enrichment scores (ES) for each pathways were determined using the following formula: ES = (# of significant metabolites in pathway(k))/total # of detected metabolites in pathway(m) / (# of significant metabolites(n))/total # of detected metabolites(N)). Then, the statistical significance was assessed using a Fisher one-sided exact test. The STITCH v5.0 beta web tool was used to investigate metabolite-protein interactions on maize endogenous pathways. The list of disturbed proteins and metabolites, including the protein EPSPS, was uploaded and the metabolic networks was studied using STITCH v5.0 initial parameters.

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Author Contributions
R.M. and S.Z.A. interpreted the data, and drafted the manuscript. V.V. performed the statistical analysis. G.R. and M.W. conducted the bioinformatics experiment. R.O.N. assisted with data interpretation. G.E.S. conceived the study. M.N.A. and M.W. conducted the proteome experiment. R.M. and S.Z.A. interpreted the data, and drafted the manuscript. V.V. performed the statistical analysis. G.E.S. conceived the study. M.N.A. and M.W. conducted the bioinformatics experiment. R.O.N. assisted with data interpretation. G.E.S. conceived the study. M.N.A. coordinated the investigation and drafted the manuscript. All authors reviewed the manuscript.

Additional Information
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Molecular profiles reveal major differences in composition between a GMO corn and its non-GMO parent

Findings question industry and regulatory position of “substantial equivalence” and have safety implications

Summary

A new peer-reviewed study led by Dr Michael Antoniou at King's College London describes the effects of the process of genetic engineering on the composition of a genetically modified Roundup-resistant GMO corn variety, NK603. In-depth analysis of types of proteins (“proteomics”) and small biochemical molecules (“metabolomics”) revealed major compositional differences between NK603 and its non-GMO parent. The results obtained show not only disturbances in energy utilisation and oxidative stress (damage to cells and tissues by reactive oxygen), but worryingly large increases in certain substances (polyamines). Polyamines found to be present in increased amounts in GMO NK603 corn include putrescine and cadaverine, which can produce various toxic effects. For example, they enhance the effects of histamine, thus heightening allergic reactions, and both have been implicated in the formation of carcinogenic substances called nitrosamines. Overall, the findings of this study disprove industry and regulatory agency claims that NK603 is ‘substantially equivalent’ to its non-GMO counterpart and suggest that a more thorough evaluation of the safety of consuming products derived from this GMO corn on a long term basis should be undertaken.

Background to study

1. The establishment of compositional ‘substantial equivalence’ is a key starting point requested by regulatory agencies for assessing the safety of a GMO crop and food. If analysis for nutrients and known toxins shows that the composition of a GMO crop is found to be in a similar range to that present in a corresponding, genetically similar non-GMO variety (often the non-GMO parent), then it is deemed to be ‘substantially equivalent’ and to require little, if any, further safety testing, especially in the USA.
2. Genetically modified (GM) corn NK603, engineered to survive being sprayed with glyphosate based weedkillers such as Roundup, was assessed as ‘substantially equivalent’ to its non-GM parent corn variety, based on a nutrient composition analysis of both crops. It was subsequently granted market approval.
3. However, the nutrient compositional analysis is relatively crude and may miss subtle yet important differences between the GMO and non-GMO food, which could have health consequences for the consumer. For example, the compositional analysis includes measurement of total protein content, yet this is less important than the profile of different types of proteins. In other words, the message is in the detail, yet this detail is currently lacking in regulatory analysis investigating the substantial equivalence of a product.
4. This gap in compositional information for the Roundup-tolerant NK603 corn was addressed in this study by analysing this GMO with the nearest non-GMO corn variety as a control. The two crops were grown under similar conditions, in the same location and season, spaced at a sufficient distance to avoid cross-contamination. One field of NK603 was sprayed once with Roundup, whilst another field of NK603 was not treated with Roundup. Samples were produced in two cultivation cycles over two growing seasons. Thus all precautions were taken to minimise environmental factors that could influence the
composition of the crops. The result is a comparative analysis that specifically highlights the effect of the genetic modification (GM) transformation process.

5. Rats fed this GMO corn over 2 years presented signs of a higher incidence of liver and kidney damage (Séralini et al., Environmental Sciences Europe, 26:14) compared with controls.

**Analytical methods used**

Analytical methods collectively known as “omics” technologies can be used to obtain an in-depth, molecular composition profile of a biological system/substance. These technologies include transcriptomics (gene function profile), proteomics (protein type profile) and metabolomics (small biochemical metabolite profile). Unlike gross nutrient analysis, omics technologies provide highly detailed molecular composition and biological functional information with a very high degree of predictability of health or disease status. In this study Dr Antoniou and colleagues have undertaken proteomics (protein profiling) and metabolomics (small biochemical profiling) analyses, comparing NK603 with its non-GMO counterpart in order to deepen the understanding of the effects of the GM transformation process used to generate this variety of GMO corn. In addition, NK603 cultivated either with or without being sprayed with Roundup was also investigated in order to determine the effects, if any, of this weedkiller on the biochemistry and hence composition of this GMO corn.

This broad range of analysis is designed to ascertain more deeply and precisely whether NK603 is truly ‘substantially equivalent’ to its corresponding non-GMO variety and whether this raises any health concerns.

**Findings**

1. A total of 117 proteins and 91 small molecule biochemicals (metabolites) were found to be statistically significantly altered in NK603 corn by the GM transformation process.
2. The GM transformation process was the major contributor to variation in the protein and metabolite profiles, rather than environmental factors such as the spraying of the Roundup weedkiller or the growing season.
3. Alteration in the protein profile revealed by the proteomics analysis was reflective of an imbalance in energy utilisation and oxidative stress (damage to cells and tissues by reactive oxygen).
4. Small molecule biochemical profile differences revealed by metabolomics mostly consisted of an increase in a class of compounds known as polyamines; the levels of potentially toxic putrescine and especially cadaverine were markedly increased in the GM NK603 corn.

**Conclusions**

1. GM NK603 corn and its corresponding non-GMO corn variety are not substantially equivalent.
2. The GM transformation process caused alterations in both protein and metabolite composition profiles in NK603 corn.
3. The non-substantial equivalence of NK603 corn with the corresponding non-GMO corn, and the increases in potential toxic compounds (polyamines; putrescine, cadaverine) in NK603 corn, indicate that a more thorough investigation of the safety of consuming products derived from this GMO food is warranted.
Relevance to health

The GM transformation process causes a general disturbance in the GMO plant. Whether the increased levels of cadaverine and putrescine found in the NK603 corn samples can account for the signs of potential negative health effects in rats fed on this corn needs to be further analysed in long-term feeding studies on laboratory animals, using methods that specifically and more accurately quantify the amounts of these polyamines and their effects.

State-of-the-art molecular profiling ‘omics’ methods could be used to deepen our understanding of the differences between GM plants and their non-GMO counterparts. This would enable scientists to improve the pre-commercial safety testing of GM plants by highlighting the presence of increased levels of known toxins (for example, certain polyamines found at increased levels in this study) or novel toxins and potentially allergenic substances.

Quote

“Our study clearly shows that the GM transformation process results in profound compositional differences in NK603, demonstrating that this GMO corn is not substantially equivalent to its non-GMO counterpart. The marked increase in putrescine and especially cadaverine is a concern since these substances are potentially toxic, being reported as enhancers of the effects of histamine, thus heightening allergic reactions, and both have been implicated in the formation of carcinogenic nitrosamines with nitrite in meat products. Our results call for a more thorough evaluation of the safety of NK603 corn consumption on a long-term basis.” Dr Michael Antoniou, study lead

The paper:


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Multiomics reveal non-alcoholic fatty liver disease in rats exposed to an ultra-low dose of Roundup herbicide

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Abstract

The impairment of liver function by low environmentally relevant doses of glyphosate-based herbicides (GBH) is still a debatable and unresolved matter. Previously we have shown that rats administered for 2 years with 0.1 ppb (50ng/L glyphosate equivalent dilution; 4ng/kg body weight/day daily intake) of a Roundup GBH formulation showed signs of enhanced liver injury as indicated by anatomorphological, blood/urine biochemical changes and transcriptome profiling. Here we present a multiomic study combining metabolome and proteome liver analyses to further confirm and obtain further insight into the Roundup-induced pathology. Out of 1906 proteins and 673 metabolites measured, a total of 254 proteins and 73 metabolites had their levels significantly altered. Proteins significantly disturbed were involved in oxoacid metabolism and fatty acid β-oxidation. Proteome disturbances reflected peroxisomal proliferation, steatosis and necrosis. The metabolome analysis confirmed lipotoxic conditions and oxidative stress by showing an activation of glutathione and ascorbate free radical scavenger systems. Also, we found metabolite alterations associated hepatotoxicity biomarkers such as γ-glutamyl dipeptides, acylcarnitines, and proline derivatives. Overall, metabolome and proteome disturbances showed a substantial overlap with hallmarks of non-alcoholic fatty liver disease and its progression to steatohepatosis and thus confirm liver functional dysfunction resulting from chronic ultra-low dose GBH exposure.

Keywords

Glyphosate, proteome, metabolome, chronic toxicity, non-alcoholic fatty liver disease
Introduction

Glyphosate-based herbicides (GBH), such as Roundup, are the major pesticides used worldwide 1. Residues of GBH are routinely detected in foodstuffs 2,3 and drinking water 4. Epidemiological data on the human body burden of GBH residues is very limited but evidence suggests that glyphosate and its metabolites are wide-spread 5. The active principle of GBH, glyphosate, is a competitive inhibitor of phosphoenolpyruvate 6. Glyphosate acts as a herbicide by inhibiting 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) of the shikimate aromatic amino acid biosynthesis pathway present in plants and some bacteria 7. Since this pathway is absent in vertebrates, glyphosate is considered to be safe for mammals.

A number of toxicity studies have shown that glyphosate and its commercial formulations have non-target effects on mammalian metabolism and provoke toxic effects especially with respect to liver and kidney structure and function 8,9. Potential adverse hepatic effects of glyphosate were first observed in the 1980s, including its ability to disrupt liver mitochondrial oxidative phosphorylation 10. As glyphosate can act as a protonophore increasing mitochondrial membrane permeability to protons and Ca\(^{2+}\) 11, it can trigger the production of reactive oxygen species resulting in observed oxidative stress 12. Elevation in oxidative stress markers is detected in rat liver and kidney after subchronic exposure to GBH at the United States permitted glyphosate concentration of 700µg/L in drinking water 13. Hepatic histological changes and alterations of clinical biochemistry are detected in rats consuming 4.87 mg/kg bw glyphosate every 2 days over 75 days 14. In farm animals, elevated glyphosate urinary levels are correlated with alterations in blood serum parameters indicative of liver and kidney oxidative stress and depletion in nutrient trace element levels 15.

Nevertheless, it should be noted that most results from these GBH toxicity studies were obtained at doses far greater than general human population exposure. Doses tested were typically over the glyphosate acceptable daily
intake (ADI), which is currently set at 0.3 mg/kg bw/day within the European Union and 1.75mg/kg bw/day in the USA based on hepatorenal toxicity measurements after chronic exposure in rats \^{16,17}. However, no long-term studies investigating the toxicity of complete GBH commercial formulations, which contain a broad spectrum of largely undisclosed “adjuvants” as well as glyphosate, have been conducted (see \^{9}). In an effort to address this gap in commercial GBH toxicity evaluation, a 2-year study was conducted where rats were administered with a Roundup GBH via drinking water at a concentration of 0.1ppb (0.05 μg/L glyphosate; daily intake 4ng/kg bw/day), which is an admissible concentration within the European Union (0.1μg/L) and USA (700μg/L) \^{18}. The results showed that Roundup caused an increased incidence in signs of anatomical pathologies, as well as changes in urine and blood biochemical parameters suggestive of liver and kidney functional insufficiency \^{19}.

Most pesticides exert their toxic effects by targeting proteins and modulating their activity. Herbicides act mostly by inhibiting plant enzymes responsible of photosynthesis, carotenoid synthesis, or amino acid synthesis \^{20}. Besides its well known interaction with EPSPS, it has been suggested that glyphosate could act on mitochondrial metabolism by inhibiting succinate dehydrogenase \^{21}, or on steroid metabolism by inhibiting aromatase enzyme activity \^{22}. Molecular profiling techniques can be used to identify specific signatures of chemical toxicity and organ pathological status \^{23,24}. The proteome and metabolome are very sensitive to toxic chemical exposures and have been used to reveal non-targets effects of herbicides such as paraquat \^{25}, atrazine \^{23} and organophosphate mixtures \^{26} in mammalian species. However, while transcriptome profiles reveal pathway disturbances that could be correlated to toxic effects, they do not always translate into alterations in protein levels and functional, metabolic disturbances. Overall, mRNA transcript abundance explains approximately one- to two-thirds of the variance in steady-state protein levels \^{27}. In yeast subjected to oxidative stress, a post-transcriptional regulation of a large fraction of the genes was observed independently of their up- or downregulation \^{28}. 
Given the insight molecular profiling methods can potentially provide into processes and mechanisms of toxicity, we have previously conducted a transcriptomics investigation of the same female cohort of animals subjected to ultra-low dose Roundup exposure, and which showed signs of liver and kidney damage at a anatomorphological and blood/urine biochemical level of function 19. Our results showed alterations in the liver transcriptome reflective of fibrosis, necrosis, phospholipidosis, mitochondrial membrane dysfunction and ischemia 29. However, as changes in the transcriptome may not fully translate into changes in the proteome and metabolome, we present here a follow-up of this gene expression profile analysis with a proteomics and metabolomics investigation of the same liver tissues. Proteins whose levels were altered were reflective of oxidative stress and fatty acid metabolism changes. Proteome alterations were typical of disturbances measured in cases of peroxisomal proliferation, steatosis and necrosis. Metabolome analysis confirmed the induction of oxidative stress, and revealed alterations in biomarkers of hepatotoxicity. Overall, metabolome and proteome disturbances showed a substantial overlap with hallmarks of non-alcoholic fatty liver disease (NAFLD) and thus confirm metabolic dysfunction resulting from chronic exposure to an ultra-low dose of Roundup.

**Results**

The female rat liver tissues, which formed the starting material for this investigation, were as previously described 29. They were obtained from animals that formed part of a 2 year study of Roundup toxicity 18. Harlan Sprague–Dawley rats were administered with Roundup via drinking water at a regulatory admissible dose (50 ng/L glyphosate). The average daily intake of Roundup was at an approximately 4 ng/kg bw/day of glyphosate equivalent dose. Control and Roundup-treated animals were respectively euthanized at 701 +/- 62 and 635 +/- 131 days.
The proteome discovery study consisted of a comparison between control (n = 10) and Roundup treated (n = 10) rat liver samples. Fractions for both non-enriched peptide and enriched phosphopeptides were analysed using Orbitrap Velos-Pro. A total of 1906 peptides were quantified across all liver samples. We began our analysis by looking at the variance structure in an unsupervised Principal Component Analysis (PCA). While percentages of explained variance on the 2 first components were low (22.3 and 14.3% respectively), a separation was observed between control and Roundup-treated rats (Figure 1A). Of the 1906 quantifiable peptides taken forward for bioanalytical analysis, 254 were respectively found to be significantly regulated (Supplementary Table 4). Figure 1B shows the statistical significance of differential protein expression by volcano plot along with respective fold changes (FC).

We developed a high throughput Tandem Mass Tag - Selected Reaction Monitoring (TMT-SRM) method to verify the alterations observed in protein levels in liver of Roundup-treated rats. The raw discovery LC-MS/MS spectra from Orbitrap Velos-Pro were used to select transition ions for each peptide (Figure 2). First, in order to determine a subset of peptides, which can be detected by SRM, individual liver samples marked by a heavy TMT were combined with an internal standard constituted by all 20 samples marked by a light TMT (Supplementary Table 5). This method was repeated 4 times and any peptides/transitions, which were not detected in all 4 repeats removed. A total of 9 proteins and 10 peptides have been analysed over a 35 minute gradient. Then, 20 combined (TMTLight and TMTHeavy) liver samples were analysed on the TSQ Vantage in triplicate, leading to the production of 60 raw data files. The average CV value between technical repeats was 13.8%. Of the 10 peptides we aimed to quantify, 5 peptides were successfully detected across all 60 replicates. Several light and heavy transitions co-eluting at the same retention time were clearly identified, as illustrated for the peptide ‘ILTFDQLALESPK’ of the 60S ribosomal protein L18 (Figure 3). All of 5 peptides showed corresponding fold changes between the two methods (Table 3). The SRM data therefore corroborate protein alterations detected in the initial discovery analysis.
In order to get an insight into the biological significance of the proteome alterations, we next conducted an enrichment analysis integrating annotations from KEGG and Gene Ontology (GO) databases using DAVID 6.7. A total of 3 major affected protein networks were identified. The most enriched group was related to the metabolism of carboxylic acids, in particular oxoacids (FE=6.2, BH corrected p= 2.6E-13). This group was constituted by 32 proteins. Out of these 32 proteins, 31 were found to be overexpressed. Since glyphosate is an oxoacid, this first set of proteins could constitute a signature of glyphosate metabolic effects. This is consistent with the glyphosate metabolic process (GO:0018920), which is defined as a type of oxoacid metabolic process (GO:0043436) in the GO database. Proteins disturbed by glyphosate included enzymes from the TCA cycle such as the pyruvate carboxylase, isocitrate dehydrogenase and fumarate hydratase. The second most significant cluster of annotation was related to fatty acid β-oxidation (FE=15.3, BH corrected p=4.9E-02), which is typically increased in Non-alcoholic Fatty Liver Disease (NAFLD). Also, 2 peptides from the microsomal triglyceride transfer protein were found upregulated. A third major cluster is indicative of response to xenobiotic stimulus (FE=15.3, BH corrected p=4.9E-02). Some P450 cytochromes had their levels altered by the Roundup treatment, namely CYP2C12, CYP2C7, CYP2C70 and CYP2E1 were overexpressed. Additionally, the metabolism of glutathione (term GO:0006749) was significantly altered (FE=15, BH corrected p=0.05). Altogether, these clusters were indicative of a change in lipid metabolism provoked by the intoxication with the Roundup herbicide. These data correlate with the increased levels of serum triglycerides shown by the biochemical analysis. The toxicity processes analysis in Metacore (Figure 4) confirms lipotoxic conditions as revealed by disturbances in protein expression associated with the induction of peroxisomal proliferation (n=13, BH corrected p= 3.3 x 10^{-5}), steatosis (n=16, BH corrected p= 5.1 x 10^{-4}) and necrosis (n=17, BH corrected p= 3.1 x 10^{-3}).
We next conducted a metabolome profiling of liver sections from the same animals to investigate for the presence of markers of liver disease. Instrument variability determined by calculating the median relative standard deviation (RSD) for the internal standards was 6%. Overall process variability determined by calculating the median RSD for all endogenous metabolites was 12%. In total, 673 compounds were identified. Data for two liver samples (one for the control group and one for the treated group) displayed extremely high concentration of numerous compounds and noticeably stood out as outliers. Statistical tests were done excluding these two outliers. Calculations were performed using natural log-transformed scaled imputed data to identify biochemicals that differed significantly. In total, 73 compounds met the statistical cut-off threshold ($p \leq 0.05$) (Supplementary Table 6). This number of altered metabolites in itself reveals a significant metabolic effect caused by the treatment based on the assumption that 5%, or approximately 35 per 700 compounds, will be significantly different due to random chance alone. Statistically significant metabolites had FC values ranging from -3.84 (1-palmitoylglycerophosphoserine) to 5.24 (2-hydroxyhippurate). Of the 73 metabolites having their levels altered, 13 had FC over 2. Glyphosate (N-(phosphonomethyl) glycine) and its principal metabolite aminomethylphosphonic acid (AMPA) were not detected in liver tissue with a limit of detection of 7.8 ppb.

Biochemicals indicative of a change in cellular redox status were markedly disturbed (Table 3; Figure 5). Ophthalmate, an analogue of reduced glutathione (GSH), was significantly increased (FC = 3.54, $p=0.0132$), while GSH depletion did not reach statistical significance (FC = -1.79, $p=0.09$). In addition, 2-aminobutyrate, which is used in the biosynthesis of ophthalmate, is also increased (FC = 1.98, $p=0.0344$). Gamma glutamyl dipeptides, indicators of the production of reduced glutathione, are increased in our study. Out of 10 gamma glutamyl dipeptides detected, 9 had their levels elevated (3 being significantly increased). Remarkably, cysteine levels (used to synthesize glutathione) were depleted (FC = -2.13, $p=0.04$). Furthermore, because hypotaurine production is dependent on cysteine levels, its decrease (FC = -2.08, $p=0.01$) suggests a redistribution of cellular cysteine stores toward...
glutathione synthesis that could deplete hypotaurine synthesis by substrate attrition. Cellular redox status disturbances are also corroborated by alterations in ascorbate metabolism (Figure 5), another intracellular free radical scavenger. Dehydroascorbate (FC = 1.26, p=0.0451) and oxalate (FC = 1.63, p=0.0162) levels were increased by the consumption of Roundup. Altogether, alterations in biochemical levels of the two major intracellular free radical scavenger systems consistently reflect cellular oxidative stress.

Higher levels of amino acids such as glycine (FC = 1.27 p=0.002) and aspartate (FC = 1.47 p=0.02), and of amino acid catabolites such as 2-aminoadipate (FC = 1.34 p=0.04) were observed. In addition, many biochemicals associated with purine and pyrimidine metabolism were elevated, indicating heightened nucleic acid turnover. Levels of purine catabolites such as urate and allantoin or pyrimidine catabolites such as β-alanine and 3-aminoisobutyrate were either not detected or not altered, suggesting that an elevation in the levels of these compounds was indicative of nucleic acid turnover associated with growth rather than nucleic acid breakdown. The liver of female rats treated with Roundup also presented with an increased rate of polyamine synthesis, suggesting cell proliferation and organ regeneration. All of the 4 polyamines detected namely acisoga (FC = 1.77, p=0.11), putrescine (FC = 1.91, p=0.03), spermidine (FC = 1.57, p=0.004) and 5-methylthioadenosine (FC = 1.73, p=0.019) were increased, with the latter 3 displaying a statistically significantly disturbance. This biochemical signature most likely indicates that overall metabolism was higher in Roundup-treated animals.

Levels of proline derivatives were elevated in the liver of Roundup-treated rats. In particular, N-methylproline levels, a biomarker of fibrosis, was increased by 2.35-fold (p=0.0018) (Figure 5). We also noticed alterations in nicotinate and nicotinamide metabolism intermediates. Levels of nicotinamide riboside (FC = -3.0, p=0.001) and nicotinamide ribonucleotide (FC = -2.5, p=0.01) were decreased. Hepatic acylcarnitines, reflective of mitochondrial fatty acid oxidation impairment, were increased. We also observed an
increased trend in hepatic accumulation of most medium and long-chain fatty acids as well as branched or dicarboxylate fatty acids. However, cholesterol levels were weakly disturbed (FC = 1.15, p=0.004) (Figure 5).

Collectively, alterations of the proteome and the metabolome profiles in the liver of rats receiving an environmental concentration of Roundup in their drinking water show substantial overlap with those characteristic of non-alcoholic fatty liver disease.

**Discussion**

We report here the first in vivo multiomic analysis combining the proteome and metabolome profiles of the livers from rats following long-term (2-year) exposure to a GBH (Roundup) at an environmentally relevant dose (50ng/L glyphosate equivalent concentration; 4ng/kg bw/day). Our integrated analysis of these molecular profiles is clearly reflective of features of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatosis (NASH). Our study thus confirms the increased incidence of liver pathologies in these female rats, which was observed at an anatomorphological and blood/urine biochemical level 18, and following transcriptome analysis 29.

NASH results from a two-hit process 30. The first hit is a metabolic disruption, marked by a hepatocellular accumulation of fatty acids, which then sensitizes the liver to further injury. Steatosis is associated with the accumulation of lipotoxic intermediates such as acylcarnitines. In liver of rats administered with Roundup, a trend in the accumulation of most fatty acids, in particular acylcarnitines, as well as a statistically significant elevation of cholesterol levels was observed (Table 3). Proteome profiles further confirmed a marked change in lipid detoxifying metabolic processes (Table 1, Figure 4). In the pathology of NASH, oxidative stress acts as a second hit 30, leading to lipid peroxidation, mitochondrial damage, hepatocellular injury, and finally chronic inflammation and fibrosis. Proteome profiles were significantly
enriched in features of peroxisomal proliferation, liver steatosis and necrosis (Figure 4). An association to features of NASH is further supported by enhancement of markers of oxidative stress and fibrosis in the metabolome profile (Table 3). The metabolomics analysis also indicates the presence of cell division. Tissue homeostasis relies on a delicate balance between apoptosis and cellular proliferation. When oxidative stress provokes apoptosis, injured cells are generally replaced through increased proliferation.

Our observations may have human health implication since NAFLD is predicted to be the next major global epidemic. Approximately 20-30% of the population in the United States carry extra fat in their livers. NAFLD is associated with the recent rapid rise in the incidence of diabetes, obesity, and metabolic syndrome. Overall, it is acknowledged that NAFLD is mostly caused by excess caloric intake, but also from consumption of processed foods, which increase simple sugar and saturated fat ingestion as well as sedentary lifestyles. However, other contributory factors, such as exposure to physiologically active environmental pollutants via contaminated food, cannot be excluded. Recently, some endocrine disrupting chemicals have been implicated in the aetiology of metabolic syndrome. Commonly defined as obesogens, some environmental chemicals have been found to promote adipose cell differentiation and lipid storage in experimental animals and thus presumably also in humans.

We detected metabolic alterations well below the glyphosate ADI (0.3 mg/kg bw/day) set within the European Union, and is within the range admitted in drinking water (0.1 ppb) and foodstuffs (for example, 20 ppm in soybeans or 2 ppm in bovine kidneys). However, inter-species biological relevance still needs to be ascertained because there is a lack of data pertaining to biological effects of glyphosate in human tissues at these levels to support or contradict our data.

The Roundup-induced liver pathologies confirmed in this report may arise from multiple sources as there is increasing evidence to suggest that GBHs and glyphosate can bring about toxic effects via different mechanisms.
depending upon the level of exposure. Glyphosate has been suggested to act as an estrogen agonist based on assays in cultures of human breast cancer cells at comparable concentrations to the native hormone \textsuperscript{36,37}. Other studies, albeit at much higher doses, have also shown that glyphosate can uncouple liver mitochondrial oxidative phosphorylation \textsuperscript{10}. Glyphosate is also a patented antibiotic (Patent No: US 7771736) and can inhibit the growth of susceptible bacteria by inhibition of the shikimate pathway and could cause dysbiosis in the gastrointestinal tract \textsuperscript{38}. Additionally, because glyphosate herbicidal action results from competition for phosphoenolpyruvate (PEP) in plants, it is possible that similar effects are being exerted by this compound on other PEP utilizing enzymes including those in mammals. This could explain the effects of glyphosate on the activity of some TCA cycle enzymes observed in this study such as pyruvate carboxylase, isocitrate dehydrogenase and fumarate hydratase (Supplementary Table 4). In this regard the fact that glyphosate has been shown to interact with mitochondrial succinate dehydrogenase (SDH) \textsuperscript{21} is noteworthy. We hypothesize that glyphosate could interfere at multiple points within the TCA cycle by inhibiting enzymes having oxoacids as substrates. Additionally, changes observed in the levels of enzymes involved in energy metabolism (for instance L-lactate dehydrogenase) as revealed by the proteome analysis (Supplementary Table 4), could also be due to the anoxic cellular status associated with NAFLD \textsuperscript{39}. In this case, aerobic respiration is compromised and replaced with anaerobic metabolism to ensure adequate ATP synthesis. However, the existence of such direct mechanisms of interference at the low environmental dose tested here currently remains unknown and thus needs further exploration.

Although our results cannot provide insight into the mechanisms of the pathologies resulting from chronic very low–dose glyphosate exposure, they highlight the need for future GBH toxicity studies where organ molecular profiles are determined prior to appearance of the overt pathologies observed at late-stage termination as in this instance. Indeed, the use of aged animals may have enhanced variability.
An important consideration is that Roundup is not a single compound, but a mixture of an active ingredient (glyphosate) combined with various adjuvants, which are required to stabilise and allow penetration of glyphosate into plants. In short term acute exposures, some adjuvants can be considered as responsible of Roundup toxicity \(^{40}\). However, as adjuvant composition is proprietary and not fully disclosed, it is not possible to attribute the toxicity of the whole agricultural herbicide formulation to a given component. Future studies involving the administration of glyphosate alone would shed light on this issue.

**Conclusions**

The results of the study presented here indicate that chronic consumption of extremely low levels of a GBH formulation (Roundup), at admissible glyphosate-equivalent concentrations, are associated with marked alterations of the liver proteome and metabolome. These changes in molecular profile overlap substantially with hallmarks of NAFLD and its progression to NASH. These alterations correlate with the observed signs of hepatic anatomorphological and biochemical pathological changes in this organ \(^{18}\), and as suggested by transcriptome profiling \(^{29}\). Confirmatory studies incorporating testing principles from endocrinology should be performed to investigate potential implications of GBH low dose exposure in the development of metabolic syndrome.

**Methods**

*Experimental design*

The rat tissues analysed in this study were obtained from animals as previously described \(^{18}\). Briefly, the experimental protocol was as follows. Following 20 days of acclimatization, Harlan Sprague-Dawley rats at 5 weeks of age were randomly assigned on a weight basis into groups of 10 animals. Animals were fed with the standard diet A04 (Safe, France) including 33% maize DKC 2675 over two years. All feed formulations consisted of a
balanced diet, chemically measured as substantially equivalent. All animals were kept in polycarbonate cages (820 cm², Genestil, France). The location of each cage within the experimental room was regularly changed. The litter (Toplit classic, Safe, France) was replaced twice weekly. The animals were maintained at 22 ± 3°C under controlled humidity (45% to 65%) and air purity with a 12 h-light/dark cycle, with free access to food and water. All reagents used were of analytical grade. The animal experimental protocol was conducted in accordance with the regulations of the local ethics committee in an animal care unit authorized by the French Ministries of Agriculture and Research (Agreement Number A35-288-1). Animal experiments were performed according to ethical guidelines of animal experimentation (regulation CEE 86/609).

Groups of 10 animals had access to either plain water (control) or to the same water supplemented with 1.1x10^{-8} % of Roundup (0.1 ppb or 0.05 μg/L glyphosate equivalent dilution). The commercial formulation of Roundup used was Grand Travaux Plus (450 g/L glyphosate, approval 2020448; Monsanto, Belgium). The required level of Roundup dilution in drinking water was confirmed by measurement of glyphosate concentration by HPLC-MS/MS. Similarly, glyphosate stability in solution was studied and validated during the 7 day period between two preparations of the test treatment solutions.

**Tissue sampling**

Animals were sacrificed at the same time of day during the course of the study either to comply with animal welfare regulations to avoid unnecessary suffering (for example, resulting from 25% body weight loss, presence of tumours over 25% bodyweight, hemorrhagic bleeding, or prostration) or at the termination of the study period of 2 years. Animals were sacrificed by exsanguination under isoflurane anesthesia. Livers were divided in two and half snap frozen in liquid nitrogen/dry ice and stored at −80°C.

*Proteome profiling using Tandem Mass Tag-LC-MS/MS*
Transverse cross sectional slices of liver were lysed in 8M lysis buffer (urea, NaCl, Tri-HCl, dH2O, phosphatase and protease inhibitor) and the protein concentration of the resulting homogenate calculated using a Nanodrop protein assay (used on the A280 setting). Samples were reduced with 5 mM dithiotreitol (Sigma, UK), alkylated by treatment with 14mM iodoacetamide (Sigma) and digested with 12 µg bovine sequencing grade trypsin (Roche, Germany, Ref. 11418475001) at 37°C for 18 hours. Subsequently, peptides were purified and extracted using Waters Sep-Pak Vac 3cc 200mg tC18 cartridges (Waters, WAT054925) in accordance to with the manufacturer’s instructions before each sample was labelled by incubation with 60mM TMT10plex Isobaric Label Reagents (Thermo-Scientific, ref 90406). Labelled peptides were then purified and extracted again with the Waters Sep-Pak Vac 3cc 200mg tC18 cartridge, before being fractionated by strong cation exchange (SCX) across an increasing salt concentration using elution buffers containing different concentrations of KCl: ranging from 0mM KCl in the first fraction to 350mM KCl in the 10th fraction. A 1/10th aliquot of the eluted peptide fractions were separated and lyophilised for direct analysis by LC-MS/MS. The remaining 9/10th of column eluate was enriched for phosphopeptides using a Pierce TiO2 Phosphopeptide Enrichment and Clean-up Kit (Pierce, Prod # 88301.).

Un-enriched samples were re-suspended in 100µl of 50mM ammonium bicarbonate and F1&6, F2&7, F3&8, F4&9 and F5&10 pooled to give 5 fractions. Phosphopeptide enriched samples were re-suspended in 30µl50mM ammonium bicarbonate and pooled in the same way as the un-enriched samples to also give 5 fractions. Both enriched (8µl) and un-enriched (5µl) fractions were loaded onto a 50cm EASY-spray column (Thermo Scientific) and quantitative analysis was performed using the Orbitrap Velos-Pro mass spectrometer (Thermo Scientific) in positive ion mode. The peptides and phosphopeptides were separated by gradient elution, from 5-80% 0.1% trifluoroacetic acid in acetonitrile (5-40% from 0-100 minutes, 40-80% from 100-110 minutes), at a flow rate of 300nl/min. Mass spectra (m/z) ranging from 400-1600 Daltons was acquired at a resolution of 60,000 and the 10
most intense ions were subjected to MS/MS by HCD fragmentation with 35% collision energy.

Protein identification was performed with Proteome Discoverer 1.4 (Thermo Fisher Scientific Inc.). Raw files were imported and searched against the UniProtKB/Swiss-Prot Database using Sequest for Proteome Discoverer. Exported raw data for the two TMT10plex sets is available as Supplementary Table 1. Raw files for both enriched and un-enriched fractions were merged together in a single file search for each of the two TMT10plex sets. Precursor mass tolerance for the searches was set at 20ppm and fragment mass tolerance at 0.8ppm. The taxonomy selected was Rattus norvegicus and three enzymatic miscleavages were allowed. Dynamic modifications selected on the search were Oxidation/ +15.995Da (M), Phospho/ +79.966Da (S, T, Y) and Deamidated/ +0.984 (N, Q) and static modifications were Carbamidomethyl/ +57.021Da (C), TMT10plex/ 229.163Da (K), TMT10plex/ 229.163Da (Any N-terminus).

Only peptides with TMT reporter ion signal intensities for all ten samples were used for further bioinformatics analysis. Any duplicate peptides were removed before the data was SumScale normalised. The two normalised data files were then merged together to give one 10vs10 file comparison. Any peptides which did not have intensity values in all twenty TMT reporter ion channels were filtered out and median values were taken of the control and treated samples respectively. Log2 ratios were then calculated from these median values to determine regulation between treatment and control samples. Data were imported into Omics Explorer 3.0 (Qlucore, New York, NY, USA) for further quality control and statistical analysis. Variations from batch effect were controlled by considering the different TMT batches as covariates. A previous evaluation of different fold change (FC) rules have found that a 1.2-fold change could be regarded as indicative of a significantly varying protein in TMT-LC-MS/MS experiments 41. Data used for the functional analysis were selected at the cut off values of p < 0.01 with FC > 1.2.
Proteome verification using Tandem Mass Tag - selected reaction monitoring experiment

Samples were prepared in the same way as the discovery experiment up to the TMT labelling stage. For selected reaction monitoring (SRM) analysis the twenty individually TMT10plex Heavy labelled samples were not combined but analysed individually against a pool of the twenty liver samples labelled with TMTZero/Light Label Reagent (Thermo-Scientific) included as a single point reference sample. All labelled peptides were purified and extracted before being lyophilised prior to mass spectrometry analysis.

Peptides were selected for TMT-SRM verification based on findings from the discovery analysis. Peptides chosen were significantly regulated against parameters where peptides had to display a fold change \( \geq 1.2 \), either up or down-regulated, whilst being significant to a p-value of \( \leq 0.01 \). Peptides were re-solubilised in 2% acetonitrile/0.1% trifluoroacetic acid and 2.5µg of protein loaded onto a 50cm EASY-Spray column (Thermo Scientific) using initial gradient conditions identical to those used in the discovery experiment. The LC system was coupled to a TSQ Vantage mass spectrometer (Thermo Scientific) set in positive ion mode with Q1 and Q3 peak width settings of 1 full width at half its maximum height (FWHM). Capillary temperature (ºC), collision gas pressure (mTorr) and spray voltage (V) were set at 270, 1.2 and 1800 respectively. In order to assess peptide transition specificity and abundance and define retention times, initial optimisation was performed using the reference sample alone. Following this a combined 1:1 mix with a random Heavy TMT labelled sample was then measured. The final method contained all successful transitions for both TMT Heavy and TMT Light versions of the peptides (Supplementary Table 2; 68 transitions from 10 peptides and 9 proteins). This final method was applied in three separate injections to each Heavy labelled experimental sample, which had been mixed in a 1:1 ratio with the Light labelled reference sample. Peptides were separated over 35 minutes, using gradient elution 5-80% 0.1% trifluoroacetic acid in acetonitrile (0-5% from 0-3 minutes, 5-50% from 3-7 minutes, 50-65% from 7-30 minutes and 65-80% from 30-35 minutes) at a flow rate of 300nl/min.
Data was analysed using Skyline software \(^{42}\), with all peak matching also being visually verified. Peak area ratios between Light and Heavy transitions were generated for each sample and exported into Excel. When importing raw SRM data files from the TSQ vantage into Skyline software, a unique peak picking algorithm was used to confidently and accurately assign the best transition peaks for each peptide. Peptides were only taken forward for analysis if all assigned peaks were within a similar retention time period across all 60 samples. From the assigned peaks Skyline software was then used to produce a ‘total ratio’ between the Light and Heavy transitions for all of the 60 raw data files (3x10 control sample injection and 3x10 treated sample injections). This ‘total ratio’ value is a mean of the transition ratios, where the ratio is the comparison of the heavy transition peak areas to the light transition peak areas. The total ratio was averaged across all control and treated samples and a fold change between the two calculated. Coefficient of variation (CV) values between technical sample repeats were calculated and also averaged across control and treatment samples. Any peptides which displayed an average technical CV value higher than 15% were excluded from further analysis.

**Metabolome analysis**

Semiquantitative metabolomics analysis was performed by ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and gas chromatography-mass spectroscopy (GC-MS) at Metabolon Inc. (Durham, NC, USA) \(^{43}\).

Samples were prepared using the automated MicroLab STAR® system from Hamilton Company (Reno, NV, USA). A recovery standard was added prior to the first step in the extraction process for QC purposes. In order to remove protein, dissociate small molecules bound to protein or trapped in the precipitated protein matrix, and to recover chemically diverse metabolites, proteins were precipitated with methanol under vigorous shaking for 2 min (Glen Mills GenoGrinder, 2000) followed by centrifugation. The resulting extract was divided into five fractions: one for analysis by UPLC-MS/MS with positive ion mode electrospray ionization, one for analysis by UPLC-MS/MS
with negative ion mode electrospray ionization, one for LC polar platform, one for analysis by GC-MS, and one sample was reserved for backup. Samples were placed briefly on a TurboVap® (SOTAX Corp, Westborough, MA, USA) to remove the organic solvent. For LC, the samples were stored overnight under nitrogen before preparation for analysis. For GC, each sample was dried under vacuum overnight before preparation for analysis.

The LC-MS portion of the platform was based on a Waters ACQUITY ultra-performance liquid chromatography (UPLC) system (Waters Corp, Milford, MA, USA) and a ThermoFisher Scientific Q-Exactive high resolution/accurate mass orbitrap mass spectrometer operated at a 35,000 mass resolution, which was interfaced with a heated electrospray ionization (HESI) source. The sample extract was dried then reconstituted in acidic or basic LC-compatible solvents, each of which contained 12 or more injection standards at fixed concentrations to ensure injection and chromatographic consistency. One aliquot was analyzed using acidic positive ion-optimized conditions and the other using basic negative ion-optimized conditions in two independent injections using separate dedicated columns (Waters UPLC BEH C18-2.1×100 mm, 1.7 μm). Extracts reconstituted in acidic conditions were gradient eluted using water and methanol containing 0.1% formic acid, while the basic extracts, which also used water/methanol, contained 6.5mM ammonium bicarbonate. A third aliquot was analyzed via negative ionization following elution from a HILIC column (Waters UPLC BEH Amide 2.1×150 mm, 1.7μm) using a gradient consisting of water and acetonitrile with 10mM ammonium formate. The MS analysis alternated between MS and data-dependent MS/MS scans using dynamic exclusion and the scan range was from 80-1000 m/z.

The samples destined for analysis by GC-MS were dried under vacuum for a minimum of 18 h prior to being derivatized under dried nitrogen using bistrimethyl-silyl trifluoroacetamide. Derivatized samples were separated on a 5% diphenyl / 95% dimethyl polysiloxane fused silica column (20 m x 0.18 mm ID; 0.18 μm film thickness) with helium as carrier gas and a temperature ramp from 60° to 340°C in a 17.5 minute period. Samples were analyzed on a
Thermo-Finnigan Trace DSQ fast-scanning single-quadrupole mass spectrometer using electron impact ionization (EI) and operated at unit mass resolving power. The scan range was from 50–750 m/z.

Raw data was extracted, peak-identified and QC processed using Metabolon’s hardware and software. Raw data is available as Supplementary Table 3. Metabolites were identified by automated comparison of the ion features in the experimental samples against a reference library of more than 3000 purified standard compounds that included retention time/index (RI), mass to charge ratio (m/z), and chromatographic data (including MS/MS spectral data), and then curated by visual inspection for quality control using software developed at Metabolon. Peaks were quantified using area-under-the-curve. A data normalization step was performed to correct variation resulting from instrument inter-day tuning differences. Each compound was corrected in run-day blocks by registering the medians to equal one and normalizing each data point proportionately. Statistical significance was determined using a Welch’s two-sample t-test performed with R, (http://cran.r-project.org/).

Statistical analysis

For plotting the results, we first performed a Principal Component Analysis (PCA), using the language and statistical environment R together with the ade4 package. Statistical significance was determined using a Welch’s two-sample t-test. The resulting p-values were adjusted by the Benjamini-Hochberg multi-test adjustment method for the high number of comparisons. The aforementioned tests and volcano plots were performed using in-house R scripts. The pathway analysis was done using the Thomson Reuters MetaCore Analytical Suite and/or the NIH Database for Annotation, Visualization and Integrated Discovery Bioinformatics Resources 6.7 (DAVID) using recommended analytical parameters.

REFERENCES


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Author Contributions Statement

R.M. performed the statistical analysis, interpreted the transcriptome data, and drafted the manuscript. G.R and M.W. conducted the proteome experiment and assisted with data interpretation. G.E.S. conceived the animal feeding trial and provided tissues for analysis. M.N.A. and G.E.S. conceived the study. M.N.A. coordinated the investigation and drafted the manuscript. All authors reviewed the manuscript.

Additional Information

The authors declare they have no competing interests.
Figure Legends

Figure 1. *Wide-scale proteome profile alteration in liver of Roundup-treated female rats.* Liver from control rats and animals receiving 0.1 ppb Roundup (50ng/L glyphosate equivalent dilution; 4ng/kg body weight/day daily intake) in drinking water were subjected to a proteome analysis. **A.** PCA analysis of peptide level profiles shows a separation into groups of treated (R) and control (C) rats in liver samples. **B.** Volcano plots of the liver proteome profiles showing the log 2 fold changes and the –log10 p-values in peptide levels induced by Roundup exposure compared to controls. Data were selected at the cut off values p < 0.01 and fold change > 1.2. Red dots are showing significantly altered peptides.

Figure 2. *The raw LC-MS/MS spectra of 60S ribosomal protein L18.* The peptide “ILTFDQLALESPK” from 60S ribosomal protein L18 detected in the discovery analysis via the Orbitrap Velos-Pro is presented along with the same peptides Transition Peak Area Percentage detection from TMT-SRM analysis via the TSQ Vantage.

Figure 3. *SRM verification of peptide “ILTFDQLALESPK” from 60S ribosomal protein L18.* The TMT Heavy peptide transitions in the internal standard can be measured at the same time as the TMT Light peptide transitions in the sample of interest using the TSQ Vantage. The peak area under the transitions curves for the Light & Heavy transitions is then calculated to give a ratio specific to each sample. These are then compared between control and treated samples. This ratio change between control and treated samples can be compared in the same way that the reporter ion intensity values are in the discovery experiment. **A.** chromatogram of the sample run. **B.** Box plot showing the retention times for each of the individual 60 samples. Co-eluting light (C) and heavy transition (D) in a control sample from a TSQ Vantage raw file analysed using Skyline software. Dot plots of comparisons between the SRM validation study (E) and the discovery study (F).

Figure 4. *Toxicity ontology analysis of proteins disturbed in liver of Roundup-treated rats.* List of top 10 scoring pathway and toxicity process networks revealed by MetaCore analysis of female liver proteome profiles receiving 0.1 ppb of Roundup
in drinking water (p<0.01, fold changes > 1.2). The p-values are determined by hyper-geometric calculation and adjusted using the Benjamini-Hochberg method.

**Figure 5. Scatter plots of the major significantly altered metabolites in livers.** Levels of each metabolite from the metabolomics of livers from receiving the herbicide Roundup in their drinking water (R) were subjected to a statistical analysis by comparison to controls (C) using a Welch's two-sample t-test. A selection of metabolites showing a statistically significant change and which are of potential biological relevance are shown. *p<0.05; **p<0.01.
Table 1. Functional clustering of liver genes derived using the DAVID gene functional classification tool. The rat genome was used as a background list to calculate the p-values of each term. A total of 123 genes were recognised. The p-values were calculated according to a modified Fisher’s exact test (EASE score) and adjusted according to the Benjamini-Hochberg method. Cluster enrichment scores (ES) and fold enrichment (FE) rank overall importance (enrichment) of gene groups or the statistically most overrepresented (enriched) biological annotations. The highest classification stringency was used.

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<th>Term in DAVID</th>
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<td>mo00380:Tryptophan metabolism</td>
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Table 2. The discovery experiment is confirmed by SRM. Detected fold changes (FC) and p-values (P) of 5 of the 6 successfully analysed peptides through the SRM method are presented and compared to fold changes and p-values from the discovery experiment. The average technical repeat CV Value (%) (CV) from the SRM validation is indicated.

<table>
<thead>
<tr>
<th>Peptide Sequence</th>
<th>Protein Descriptions</th>
<th>SRM</th>
<th>Disc. Exp.</th>
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<td></td>
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<td>P</td>
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<td>aLTVPELTQQMFDAk</td>
<td>Tubulin beta-3 chain</td>
<td>1.60</td>
<td>5.3e-6</td>
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<tr>
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<td>4.6e-1</td>
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<tr>
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<td>Carbamoyl-phosphate synthase [ammonia], mitochondrial</td>
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<tr>
<td>iLTFDQLALESpk</td>
<td>60S ribosomal protein L18</td>
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<td>5.3e-5</td>
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<td>Cytochrome P450 2D26</td>
<td>1.14</td>
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</table>
Table 3. List of metabolites having their levels significantly altered by the Roundup treatment in liver. Levels of each metabolite from the metabolomics of livers from receiving the herbicide Roundup in their drinking water were subjected to a statistical analysis by comparison to controls using a Welch’s two-sample t-test. A selection of metabolites showing a statistically significant change, their mass-to-charge ratio (M/Z), as well as their fold changes and p-values is shown.

<table>
<thead>
<tr>
<th>Pubchem ID</th>
<th>Name</th>
<th>M/Z</th>
<th>FC</th>
<th>p-value</th>
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<td>0.0009</td>
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<td>0.0011</td>
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<td>611</td>
<td>glutamate</td>
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<td>557</td>
<td>N-methyl proline</td>
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<td>2.35</td>
<td>0.0018</td>
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<tr>
<td>750</td>
<td>glycine</td>
<td>101.9</td>
<td>1.27</td>
<td>0.0020</td>
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<tr>
<td>444485</td>
<td>3'-dephosphocoenzyme A</td>
<td>686.1</td>
<td>0.56</td>
<td>0.0023</td>
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<td>10253</td>
<td>2-hydroxyhippurate (salicylate)</td>
<td>194.0</td>
<td>5.24</td>
<td>0.0032</td>
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<td>gulosic acid*</td>
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<td>0.0035</td>
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<td>spermidine</td>
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<td>112072 anserine</td>
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Roundup causes non-alcoholic fatty liver disease at very low doses

Cutting edge molecule profiling analyses reveal that the popular weedkiller Roundup causes liver damage at doses permitted by regulators

A new peer-reviewed study led by Dr Michael Antoniou at King's College London using cutting edge profiling methods describes the molecular composition of the livers of female rats administered with an extremely low dose of Roundup weedkiller over a 2-year period. The dose of glyphosate from the Roundup administered was thousands of times below what is permitted by regulators worldwide. The study revealed that these animals suffered from non-alcoholic fatty liver disease (NAFLD). The study is unique in that it is the first to show a causative link between consumption of Roundup at a real-world environmental dose and a serious disease condition.

Background to current study

1. A previous study involving administration of Roundup weedkiller to rats was conducted by Gilles-Eric Seralini and colleagues.
2. This original investigation administered an extremely low, environmentally relevant dose of a commercial Roundup formulation at 0.1ppb (parts per billion)/50ppt (parts per trillion) glyphosate via drinking water for 2 years. Daily intake of glyphosate from the Roundup was 4 nanograms per kilogram of body weight per day, which is thousands of times below what is permitted by regulators (Seralini et al., 2014).
3. Analysis at an anatomical (organ) and blood/urine biochemical level suggested a higher incidence of liver and kidney damage in the Roundup treatment group compared to control animals. Liver and kidney pathologies were also present in the control group due to the advanced age of the animals, but at a lower frequency. (Seralini et al., 2014)
4. A follow up investigation of the gene function profiles of the livers and kidneys from the female animals from this same study strongly supported the observation that these organs were damaged suggesting the presence of an increased incidence of fibrosis (scarring), necrosis (areas of dead tissue), phospholipidosis (disturbed fat metabolism) and damage to mitochondria (the centres of respiration in cells) compared to control animals (Mesnage et al., 2015).

Purpose of current study

We have previously reported the gene function profile (“transcriptomics”) analysis; i.e., which genes are turned off or on and at what level, in livers and kidneys from female rats fed an ultra-low dose of Roundup (Mesnage et al., 2015). Our results supported observations at an anatomical (organ) and blood/urine biochemical level that these organs suffered an increased incidence of structure and functional damage [fibrosis (scarring), necrosis (areas of dead tissue), phospholipidosis (disturbed fat metabolism) and damage to mitochondria (the centres of respiration in cells)] compared to control animals (Mesnage et al., 2015). However, although gene function profile transcriptomics analysis is able to predict health or disease status of an organ, it does not provide definitive proof of harm. This is mainly because it does not give a direct measure of the actual biochemistry of the organ under study – and also because alterations in gene function seen in a test do not always result in changes in physical composition (proteins, small molecule biochemical) that could lead to disease.

In our new study we undertook a follow-up protein composition profile (“proteomics”) and small molecule metabolite biochemical profile (“metabolomics”) investigation of the same liver samples to confirm the prediction of disease suggested by our transcriptomics gene expression profile analysis. As the proteomics and metabolomics directly measure the actual composition of the organ, these analytical methods provide a definitive assessment of its health or disease status.

Findings

Proteins significantly disturbed (214 out of 1906 proteins detected), as shown by the proteomics profiling, reflected a type of cell damage from reactive oxygen (peroxisomal proliferation), steatosis (serious fatty liver disease) and necrosis (areas of dead tissue).

The metabolomics analysis (55 metabolites altered out of 673 detected) confirmed lipotoxic (excess fatty tissue) conditions and oxidative stress. Metabolite alterations were also associated with hallmarks of serious liver toxicity.
Overall, metabolomics and proteomics disturbances showed a substantial overlap with biochemical hallmarks of non-alcoholic fatty liver disease and its progression to steatohepatosis (serious fatty liver disease) and thus definitively confirm liver dysfunction resulting from chronic ultra-low dose Roundup exposure.

**Analytical methods**

The cutting-edge molecular composition analytical methods used were:

(i) Metabolomics: analysis of types and amounts of small molecule metabolites or chemicals within the organ or system being studied

(ii) Proteomics: analysis of the types and levels of proteins within the organ or system being studied

These omics analyses reveal *molecular signatures* that can be used to *predict* and/or *confirm* long-term toxic effects resulting from the consumption of a chemical pollutant, in this case Roundup.

**Relevance to health**

These results demonstrate that long-term consumption of an ultra-low, environmentally relevant dose of Roundup at a glyphosate daily intake level of only 4 nanograms per kilogram of body weight per day, which is 75,000 times below EU and 437,500 below US permitted levels, results in non-alcoholic fatty liver disease (NAFLD). Regulators worldwide accept toxicity studies in rats as indicators of human health risks. Therefore, the results of this latest study may have serious consequences for human health.

NAFLD currently affects 25% of the US population. Risk factors include being overweight or obese, having diabetes, high cholesterol or high triglycerides in the blood. Rapid weight loss and poor eating habits also may lead to NAFLD. However, some people develop NAFLD even if they do not have any risk factors. Symptoms include fatigue, weakness, weight loss, loss of appetite, nausea, abdominal pain, spider-like blood vessels, yellowing of the skin and eyes (jaundice), itching, fluid build-up and swelling of the legs (edema) and abdomen (ascites), and mental confusion. NAFLD can progress to the more serious condition non-alcoholic steatohepatitis (NASH). NASH causes the liver to swell and become damaged. Most people with NASH are between the ages of 40 and 60 years. It is more common in women than in men. NASH is one of the leading causes of cirrhosis in adults in the United States. Up to 25% of adults with NASH may have cirrhosis. (see [http://www.liverfoundation.org/abouttheliver/info/nafld/](http://www.liverfoundation.org/abouttheliver/info/nafld/)).

**Quote from lead author Dr Michael Antoniou:**

“The findings of our study are very worrying as they demonstrate for the first time a causative link between an environmentally relevant level of Roundup consumption over the long-term and a serious disease - namely non-alcoholic fatty liver disease. Our results also suggest that regulators should reconsider the safety evaluation of glyphosate-based herbicides.”

**The paper:**


*Communicating author: [michael.antoniou@kcl.ac.uk](mailto:michael.antoniou@kcl.ac.uk)*
Dr Michael Antoniou and Dr Robin Mesnage respond to “Expert reaction to multiomics analysis of NK603 GM maize as published in Scientific Reports”* – quotes collected by the Science Media Centre

http://www.scioncemediacentre.org/expert-reaction-to-multiomics-analysis-of-nk603-gm-maize/

Dr Dan MacLean, Head of Bioinformatics at The Sainsbury Laboratory, said:

“A big issue with this analysis is that materials were collected under potentially quite different conditions. Different parts of the same farm, potentially different chemical makeups in the soil, different water contents, different elevations, exposures and temperatures. Under tight laboratory conditions the metabolome and proteome are very variable and the statistics presented here do not go anywhere near controlling for those factors.

“There are a huge amount of things that could be affecting the expression and levels of everything in those plants and no exploratory and controlling statistics are presented. The analysis just jumps straight into ‘everything is equal, let’s do tests’ and then uses underpowered ones. Much better statistical modelling of the variables is required to allow the workers to definitively ascribe any protein/metabolome changes to any of the experimental variables supposedly under test.

“This has the effect of making the decisions about what pathways are changing moot. No clear conclusions can be reached, and certainly not on the basis of p-values. Hence all downstream analyses could not be expected to show clearly any patterns because of considerable noise in the list of things that are changing.”

Dr Michael Antoniou and Dr Robin Mesnage respond: Dan MacLean states that different growing conditions could account for the differences found between the GM and non-GM crops. However, this suggests that he has not read the paper in sufficient detail, since we state in the Materials and Methods section that all these factors were carefully controlled for, thus minimizing the possibility of their being significant contributors to the changes found in the GM crop. The soil type across all the growing areas was the same, as shown in the soil analysis in the supplementary online data (Additional File 1). The plots of land on which the different crops were grown were not sufficiently spaced to present significant differences in elevation, water content, exposures or temperature.

We also minimized the possibility that different growing seasons may be responsible for the differences. As mentioned in our article, “the fold changes observed in the comparisons of the NK603 maize sprayed with Roundup, the unsprayed NK603 maize and the isogenic control corn were highly correlated between the two cultivations performed during two different growing seasons”.

However, even though our experimental design takes into account the effect of the growing season, further experiments conducted under different environmental conditions would be needed to determine the full range of effects of the GM transformation process on this maize type.
Dan MacLean takes issue with the statistical analytical methods used. However, these methods have been used for decades to explore the significance of differences seen in biomedical research. It is widely known that errors can be made by using underpowered statistics when a study is measuring multiple variables and this is why we adjusted the p-values using the Benjamini-Hochberg multi-test method for a high number of comparisons.

The investigation we have undertaken using these established molecular profiling and statistical analytical methods solidly establishes the biological differences between the GM maize and its non-GM counterpart by looking at 1) the biochemical pathways affected in the plants, 2) the two maize cultivations, and 3) previously published studies. The results of these analyses were highly consistent and robust.

It is unclear which “experimental variables supposedly under test” Dan MacLean is referring to, because in fact only one experimental variable was under test – the effect of the GM process on this maize type.

Our experiment has established the biological differences between the GM and non-GM maize types tested, including elevated levels of two potentially toxic polyamines (putrescine and cadaverine) in the GM maize. However, the toxicological effects on the consumer are outside the scope of the study, as stated in the paper.

Dr Joe Perry, former Chair of the European Food Safety Authority GMO Panel, said:

“In contrast with compositional analysis, which is done for every application, and reported by EFSA, and which involves proper replicated field trials, this study appears to have been done with single, unreplicated plots.

“Therefore it is not possible to say with any certainty whether the differences reported are due to differences between the treatments or differences between the two fields (or two plots within the fields) used.

“In other words the basic tenets of experimental design seem not to have been followed. For that reason I could not yet describe this as a thorough piece of science.

“Further details about the conduct of the experiment would be useful to confirm or otherwise this initial impression.”

Dr Michael Antoniou and Dr Robin Mesnage respond: Joe Perry is incorrect in claiming that our study was done with single, unreplicated plots. In reality there were two cultivations of maize over two growing seasons, and the results were consistent over both, as presented.

The compositional analyses of GM crops performed by the GMO producer companies and submitted to regulators in support of market authorisation are extremely superficial, looking at major elements such as total proteins, carbohydrates and fats. They do not examine the types of proteins or metabolites that are present, yet these factors can determine whether a GM crop is substantially equivalent to the non-GM crop and safe to eat.

As we explained in response to Dan MacLean, differences between the fields in which the maize varieties were grown were controlled for and thus were not a factor in explaining the differences in the GM maize.
Prof Johnjoe McFadden, Professor of Molecular Genetics at the University of Surrey, said:

“The science is good as far as it goes. But the analysis only emphasises the inadequacy of the ‘substantial equivalence principle’. How equivalent does it need to be? If you perform this detailed level of analysis on any perturbation of any organism you will detect this level of change – organisms are extraordinary sensitive and, for example, similar changes are produced when treated with e.g. pesticide or herbicides or when attacked by pests.

“I would expect that practically any perturbation to an organism will generate a response that can be detected by these powerful techniques – that is after all what life does.

“So all it shows is that GM, like pesticides, herbicides, drought, predation or even growing in a different field will produce a response by the organism. If GM was banned on these grounds then so would all herbicide pesticides and indeed anything that causes a change (which is everything).”

Dr Michael Antoniou and Dr Robin Mesnage respond: Johnjoe McFadden seems to imply that our analysis is too detailed, but the methods employed are both cutting-edge and widely used in both research and diagnosis. He is incorrect in implying that differences in pesticide or herbicide use could be responsible for the changes in the GM maize, since these factors were taken into account. Our analysis did indeed reveal an effect resulting from the application of Roundup herbicide on the GM Roundup-tolerant maize, but this factor did not make such a large difference as the GM process itself (see Figure 2 in our paper).

In addition, we conducted a detailed analysis of pesticide residues in the GM and non-GM maize (Additional File 2) and found there were none above levels of detection. There were no differences in pesticide or fertilizer use between the GM and non-GM maize, except that Roundup herbicide was applied to one cultivation of the GM maize, in accordance with how this type of maize is designed to be grown. Therefore the differences observed in the GM maize cannot be attributed to differences in pesticide use or presence.

However, even if the toxicological relevance of the differences remains unclear, what is clear is that the use of these molecular profiling tools allows a better understanding of the composition of GM plants and thus could improve the risk assessment of the non-target effects of genetic modification. In fact, genetic engineers cannot control or predict the effects of genetic engineering on plants and currently these are not measured at the molecular level.

Thanks Michael,
And thanks to all of you! None of this could have possibly happened without the Science Communication Network. Amy, Emily, Gabi, and ALL OF YOU! We've built a virtual village over these past 15 years, and it works.

On Oct 10, 2016, at 9:59 AM, Antoniou, Michael <michael.antoniou@kcl.ac.uk> wrote:

Many congrats to Pete and Phil, richly deserved!

Michael

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Sent: 10 October 2016 14:47
To: Pete Myers <jpmyers@ehsic.org>
Cc: Amy Kostant <amy@sciencecom.org>; Terry Collins <tc1u@andrew.cmu.edu>; CranmerJoanM@uams.edu; deborah_cory-slechta@urmc.rochester.edu; pldefur@igc.org; Steve Gilbert <sgilbert@innd.org>; tyrone@berkeley.edu; Dr. Steve Heilig <heilig@sfms.org>; pathunt@wsu.edu; Richard Jackson <dickjackson@ucla.edu>; Harvey Karp <dr.karp@thehappiestbaby.com>; Landrigan, Philip <philip.landrigan@mssm.edu>; BLaanphear@sfu.ca; hlnlead@pitt.edu; Peter Orris <porris@uic.edu>; dozonoff@bu.edu; gprins@uic.edu; Ted Schettler <tschettler@igc.org>; Howard Snyder <snyderh@email.chop.edu>; Prof. Fred vom Saal <vomsalf@missouri.edu>; Bernard Weiss <bernard_weiss@urmc.rochester.edu>; WoodruffT@obgyn.ucsf.edu; tzoeller@bio.umass.edu; shuk-mei.ho@uc.edu; stahlhutr@missouri.edu; Bruce Blumberg <blumberg@uci.edu>; Sarah Vogel <svogel@edf.org>; Laura Vandenberg <lvandenberg@schoolph.umass.edu>; carl-gustaf.bornehag@kau.se; Russ Hauser <RHAUSER@hohp.harvard.edu>; Leonardo Trasande <leonardo.trasande@nyu.edu>; kkreider@unfoundation.org; Amy Itescu <itescu@UCMAIL.EDU>; Antoniou, Michael <michael.antoniou@kcl.ac.uk>; Sheldon Krimsky <sheldon.krimsky@tufts.edu>; Joseph Allen <jgallen@hsph.harvard.edu>; Andreas Kortenkamp <andreas.kortenkamp@brunel.ac.uk>; Emily Copeland <emily@sciencecom.org>; Gabriela Silvani <gabriela@sciencecom.org>
Subject: Re: Good news from NIEHS

Congratulations, Pete!! So richly deserved.

Sent from my iPad

On Oct 10, 2016, at 9:44 AM, Pete Myers <jpmyers@ehsic.org> wrote:

Its nice to be invited to the party by mainstream medicine! Thanks Amy! Been a long-time coming since Wingspread! Never, ever imagined I would be recognized by Francis Collins, for anything...

On Oct 10, 2016, at 9:35 AM, Amy Kostant <amy@sciencecom.org> wrote:

Hi All,
Just making sure you saw this news about such wonderful leaders in our field. Congratulations Pete and Phil!

Amy, Emily, and Gabi

News Release

NIH to Recognize 12 Champions of Environmental Health Research

Awards are part of the NIEHS 50th anniversary celebration. Twelve individuals will receive the first-ever Champion of Environmental Health Research Award from the National Institute of Environmental Health Sciences (NIEHS), for their significant contributions to the field.

The awards will be presented Nov. 1 at the NIEHS campus in Research Triangle Park, North Carolina, to celebrate its 50th anniversary. NIEHS is part of the National Institutes of Health, and is the only institute headquartered outside the Washington, D.C., area. NIEHS funds approximately 1,000 grants to researchers across the country each year, and has also played a key role in the economic development of North Carolina.

2016 marks 50 years since NIH began a dedicated research program to discover links between environment and health, said NIH Director Francis S. Collins, M.D., Ph.D. Its a complex research field that needs the attention of top scientists, and I congratulate these awardees for their outstanding contributions.

The champion awards recognize outstanding researchers, leaders, and communicators that have contributed to the NIEHS mission to discover how the environment affects people in order to promote healthier lives.

NIEHS and the research it has supported during the last five decades has made significant improvements to public health, said NIEHS Director Linda Birnbaum, Ph.D. From our pioneering studies showing the dangers of lead and secondhand smoke, to our more recent efforts to prevent breast cancer and other diseases, NIEHS has helped identify and reduce the environmental factors that contribute to these diseases. We couldnt have accomplished these things, without the help of many talented, dedicated people.

2016 Champion of Environmental Health Research awardees
Charles E. Blumberg
Blumberg is an architect and interior designer of research facilities with the Division of Environmental Protection at NIH. He is a principal player in the sustainable buildings movement, using science-based solutions to make buildings more supportive of human health. His influence can be seen in nearly all NIH facilities, including NIEHS. Blumberg represents NIH on the U.S. Green Building Council, championing the application of human health research and principles of sustainability in the development of building standards.

Jeffrey Gordon, M.D.
Gordon is an internationally recognized expert on the microbiome, whose pioneering studies have dramatically altered our understanding of the microbial origins of health and disease. His research for the NIH Human Microbiome Project has broken new ground in our understanding of how gut microbial communities affect intestinal growth and function, and relates directly to the core mission of NIEHS to understand how the environment influences human health, especially during the first years of life. Gordon is the Robert J. Glaser Distinguished University Professor, and director of the Center for Genome Sciences and Systems Biology at Washington University in St. Louis.

Thomas Kunkel, Ph.D.
Kunkel is a world leader in the study of DNA replication fidelity and how environmental disruptions of the process can produce cytotoxicity, mutagenesis, and adverse health effects. As an NIEHS distinguished investigator leading the Genome Integrity and Structural Biology Laboratory, Kunkels exceptional work during his 34-year career at the institute has merged biochemistry, structural biology, genetics, and genomics to help us better understand how mutations are avoided or generated. His work has broken new ground in our knowledge of DNA repair processes that operate prior to DNA replication.

Philip Landrigan, M.D.
Landrigan is a pediatrician and epidemiologist known for his many decades of work protecting children against environmental threats to health, in particular, reducing the level of childrens exposure to lead, pesticides, and other environmental contaminants. His landmark lead poisoning studies in the 1970s played a key role in phasing out lead from gasoline and the ban on lead paint. Landrigan is dean for global health, professor of environmental medicine and public health, and professor of pediatrics at the Icahn School of Medicine at Mount Sinai, New York City, as well as president of the Collegium Ramazzini.

John Peterson (Pete) Myers, Ph.D.
Myers is a biologist, and founder, CEO, publisher, and chief scientist of the nonprofit foundation Environmental Health Sciences. Through its twin online publications, Environmental Health News and The Daily Climate, Environmental Health Sciences has successfully mainstreamed science reporting. In 1996, Myers co-authored Our Stolen Future, which explores the threat of endocrine disruption to fetal development. He is an adjunct professor of chemistry at Carnegie Mellon University, Pittsburgh. He has won several awards, including the 2016 Laureate Award for Outstanding Public Service from the Endocrine Society.
Jeanne Rizzo, R.N.
As president and CEO of the Breast Cancer Fund since 2001, Rizzo has been a tireless advocate for improved public awareness of the increasingly complex science linking environmental exposure and breast cancer, helping citizens make potentially lifesaving changes in their daily routines. She has helped remove harmful chemicals from consumer products, and oversees a program that trains community activists on breast cancer science and sends them into the community to learn about peoples health needs. As co-chair of the federal Interagency Breast Cancer and Environmental Research Coordinating Committee, she helped produce the landmark 2013 report, Breast Cancer and the Environment: Prioritizing Prevention.

Kurt Straif, M.D., Ph.D.
Straif is a world-renowned epidemiologist and public health leader whose research has advanced our understanding of the occupational and environmental risk factors for cancer. He has worked for the World Health Organization International Agency for Research on Cancer (IARC) in Lyon, France, for 15 years. For the last six, he has led the IARC cancer monographs section, which alerts national health agencies to sources of potential exposure to carcinogens. He is also the scientific director of the IARC Summer School on Cancer Epidemiology. Straif was a leading force in the classification of outdoor air pollution as a carcinogen.

Allen Wilcox, M.D., Ph.D.
Wilcox is a leader in studies of reproductive epidemiology and head researcher in the NIEHS Epidemiology Branch. His work has fundamentally changed our understanding of fertility and pregnancy. He has studied the critical time period from conception to birth, and how specific environmental factors might affect reproduction and development. His current work focuses on cerebral palsy and its possible prenatal causes. He has received numerous awards for his contributions, including the 2016 NIH Directors Award. He was also a finalist for the 2016 Samuel J. Heyman Service to America medal, which highlights excellence in the federal workforce.

Champion of Environmental Health Research Awards will also be presented to four distinguished scientists who have served as leaders of the institute.

Linda Birnbaum, Ph.D.
Birnbaum has been director of NIEHS since 2009. She is an internationally recognized toxicologist, whose research has enriched our understanding of endocrine disruption and cancer, and shed new light on the environmental health risks posed by substances such as dioxins, flame retardants, polychlorinated biphenyls, and bisphenol A. Birnbaum has authored hundreds of papers, and received numerous awards, including the 2016 North Carolina Award, the states highest civilian honor for her science contributions. She is the first woman, and first toxicologist, to head NIEHS and the National Toxicology Program (NTP).

Kenneth Olden, Ph.D.
During his 14 years, from 1991 to 2005, leading NIEHS and NTP, Olden repeatedly broke new ground. As the first African-American to direct an NIH institute, he worked tirelessly to make the striking health disparities between racial and ethnic groups a research priority. He was a powerful advocate for collaboration between community groups and research
institutions to identify and address environmental health concerns. After leaving NIEHS, he became the founding dean of a new School of Public Health at Hunter College in New York City. From there, Olden served as director of the National Center for Environmental Assessment at the U.S. Environmental Protection Agency for five years.

**David Schwartz, M.D.**

Schwartz became the fourth director of NIEHS in 2005. He is world-renowned for his contribution to the understanding of the roles played by genetic determinants and environmental exposures in the onset of lung diseases, such as asthma and pulmonary fibrosis. At NIEHS, Schwartz led the institute into new arenas, such as epigenetics and exposure phenotyping through the Exposure Biology Program. He planned a new clinical research unit for NIEHS, and supported advanced technologies for sensor devices and bioinformatics. Currently, Schwartz is a professor of medicine and immunology and holds the Robert W. Schrier Chair of Medicine at the University of Colorado, Aurora.

**Samuel Wilson, M.D.**

Wilson is a leader in structural biology techniques and head researcher in the NIEHS Genomic Integrity and Structural Biology Laboratory. He also served as deputy director and twice as acting director of NIEHS and NTP. Wilson has distinguished himself as a pioneer in the use of powerful structural biology techniques to understand DNA replication. Knowledge gained through his work has fundamentally advanced our understanding of base excision repair, a key cellular defense mechanism against the effects of metabolism, inflammation, and environmental exposure. Wilson has received numerous awards, including the prestigious Ruth L. Kirschstein Mentoring Award, for his mentoring and leadership skills. In addition to the award presentations, the NIEHS 50th anniversary program, which is open to the public and being webcast from 10 a.m. to noon Nov. 1, will include several distinguished speakers, including Ira Flatow, host of Science Friday, Public Radio International; James Hunt, former governor of North Carolina; Carol Folt, Ph.D., chancellor of the University of North Carolina at Chapel Hill, and U.S. Representative David Price.

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*NIEHS supports research to understand the effects of the environment on human health and is part of NIH. For more information on environmental health topics, visit [www.niehs.nih.gov](http://www.niehs.nih.gov). Subscribe to one or more of the NIEHS news lists ([http://www.niehs.nih.gov/news/newsroom/newslist/index.cfm](http://www.niehs.nih.gov/news/newsroom/newslist/index.cfm)) to stay current on NIEHS news, press releases, grant opportunities, training, events, and publications.*

**About the National Institutes of Health (NIH):** NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit [NIH](http://www.niehs.nih.gov).

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*NIH...Turning Discovery Into Health*

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**Amy Kostant**

*Science Communication Network (SCN)*

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To: Amy Kostant <amy@sciencecom.org>
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Sent: 10/10/2016 6:44:24 AM
Subject: Re: Good news from NIEHS

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News Release
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The champion awards recognize outstanding researchers, leaders, and communicators that have contributed to the NIEHS mission to discover how the environment affects people in order to promote healthier lives.

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2016 Champion of Environmental Health Research awardees

**Charles E. Blumberg**
Blumberg is an architect and interior designer of research facilities with the Division of Environmental Protection at NIH. He is a principal player in the sustainable buildings movement, using science-based solutions to make buildings more supportive of human health. His influence can be seen in nearly all NIH facilities, including NIEHS. Blumberg represents NIH on the U.S. Green Building Council, championing the application of human health research and principles of sustainability in the development of building standards.

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**John Peterson (Pete) Myers, Ph.D.**
Myers is a biologist, and founder, CEO, publisher, and chief scientist of the nonprofit foundation Environmental Health Sciences. Through its twin online publications, Environmental Health News and The Daily Climate, Environmental Health Sciences has successfully mainstreamed science reporting. In 1996, Myers co-authored Our Stolen Future, which explores the threat of endocrine disruption to fetal development. He is an adjunct professor of chemistry at Carnegie Mellon University, Pittsburgh. He has won several awards, including the 2016 Laureate Award for Outstanding Public Service from the Endocrine Society.

**Jeanne Rizzo, R.N.**
As president and CEO of the Breast Cancer Fund since 2001, Rizzo has been a tireless advocate for improved public awareness of the increasingly complex science linking environmental exposure and breast cancer, helping citizens make potentially lifesaving changes in their daily routines. She has helped remove harmful chemicals from consumer products, and oversees a program that trains community activists on breast cancer science and sends them into the community to learn about peoples health needs. As co-chair of the federal Interagency Breast Cancer and Environmental Research Coordinating Committee, she helped produce the landmark 2013 report, Breast Cancer and the Environment: Prioritizing Prevention.

**Kurt Straif, M.D., Ph.D.**
Straif is a world-renowned epidemiologist and public health leader whose research has advanced our understanding of the occupational and environmental risk factors for cancer. He has worked for the World Health Organization International Agency for Research on Cancer (IARC) in Lyon, France, for 15 years. For the last six, he has led the IARC cancer monographs section, which alerts national health agencies to sources of potential exposure to carcinogens. He is also the scientific director of the IARC Summer School on Cancer Epidemiology. Straif was a leading force in the classification of outdoor air pollution as a carcinogen.

**Allen Wilcox, M.D., Ph.D.**
Wilcox is a leader in studies of reproductive epidemiology and head researcher in the NIEHS Epidemiology Branch. His work has fundamentally changed our understanding of fertility and pregnancy. He has studied the critical time period from conception to birth, and how specific environmental factors might affect reproduction and development. His current work focuses on cerebral palsy and its possible prenatal causes. He has received numerous awards for his contributions, including the 2016 NIH Directors Award. He was also a finalist for the 2016 Samuel J. Heyman Service to America medal, which highlights excellence in the federal workforce.

Champion of Environmental Health Research Awards will also be presented to four distinguished scientists who have served as leaders of the institute.

**Linda Birnbaum, Ph.D.**
Birnbaum has been director of NIEHS since 2009. She is an internationally recognized toxicologist, whose research has enriched our understanding of endocrine disruption and cancer, and shed new light on the environmental health risks posed by substances such as dioxins, flame retardants, polychlorinated biphenyls, and bisphenol A. Birnbaum has authored hundreds of papers, and received numerous awards, including the 2016 North Carolina Award, the states highest civilian honor for her science contributions. She is the first woman, and first toxicologist, to head NIEHS and the National Toxicology Program (NTP).
Kenneth Olden, Ph.D.
During his 14 years, from 1991 to 2005, leading NIEHS and NTP, Olden repeatedly broke new ground. As the first African-American to direct an NIH institute, he worked tirelessly to make the striking health disparities between racial and ethnic groups a research priority. He was a powerful advocate for collaboration between community groups and research institutions to identify and address environmental health concerns. After leaving NIEHS, he became the founding dean of a new School of Public Health at Hunter College in New York City. From there, Olden served as director of the National Center for Environmental Assessment at the U.S. Environmental Protection Agency for five years.

David Schwartz, M.D.
Schwartz became the fourth director of NIEHS in 2005. He is world-renowned for his contribution to the understanding of the roles played by genetic determinants and environmental exposures in the onset of lung diseases, such as asthma and pulmonary fibrosis. At NIEHS, Schwartz led the institute into new arenas, such as epigenetics and exposure phenotyping through the Exposure Biology Program. He planned a new clinical research unit for NIEHS, and supported advanced technologies for sensor devices and bioinformatics. Currently, Schwartz is a professor of medicine and immunology and holds the Robert W. Schrier Chair of Medicine at the University of Colorado, Aurora.

Samuel Wilson, M.D.
Wilson is a leader in structural biology techniques and head researcher in the NIEHS Genomic Integrity and Structural Biology Laboratory. He also served as deputy director and twice as acting director of NIEHS and NTP. Wilson has distinguished himself as a pioneer in the use of powerful structural biology techniques to understand DNA replication. Knowledge gained through his work has fundamentally advanced our understanding of base excision repair, a key cellular defense mechanism against the effects of metabolism, inflammation, and environmental exposure. Wilson has received numerous awards, including the prestigious Ruth L. Kirschstein Mentoring Award, for his mentoring and leadership skills.

In addition to the award presentations, the NIEHS 50th anniversary program, which is open to the public and being webcast from 10 a.m. to noon Nov. 1, will include several distinguished speakers, including Ira Flatow, host of Science Friday, Public Radio International; James Hunt, former governor of North Carolina; Carol Folt, Ph.D., chancellor of the University of North Carolina at Chapel Hill, and U.S. Representative David Price.

NIEHS supports research to understand the effects of the environment on human health and is part of NIH. For more information on environmental health topics, visit www.niehs.nih.gov. Subscribe to one or more of the NIEHS news lists (http://www.niehs.nih.gov/news/newsroom/newslist/index.cfm) to stay current on NIEHS news, press releases, grant opportunities, training, events, and publications.

About the National Institutes of Health (NIH): NIH, the nation’s medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit NIH.

Amy Kostant
Science Communication Network (SCN)
0: 301-654-6665
C: 202-255-6665
amy@sciencecom.org

NIH...Turning Discovery Into Health
Hi Pete-

I am not a 'reply all' kind of girl, but I wanted to tell you that hearing that you have been awarded Sierras Distinguished Service Award not only made my day, but got the whole week off to a great start. Your enthusiasm and unflagging dedication to making the world a better place has been a constant source of strength for me. It is easy to become pessimistic in the face of great odds, but you always focus energy on finding new ways to bring change. You are truly deserving of this recognition.

With warm congratulations,

Pat
Thank you Pat!

Your reaction made MY day!

On Aug 7, 2017, at 1:39 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hi Pete-

I am not a 'reply all' kind of girl, but I wanted to tell you that hearing that you have been awarded Sierras Distinguished Service Award not only made my day, but got the whole week off to a great start. Your enthusiasm and unflagging dedication to making the world a better place has been a constant source of strength for me. It is easy to become pessimistic in the face of great odds, but you always focus energy on finding new ways to bring change. You are truly deserving of this recognition.

With warm congratulations,

Pat
From: Pete Myers <jpmyers@ehsic.org>
To: Bruce Blumberg <blumberg@uci.edu>
CC: Amy Kostant <amy@sciencecom.org>, Philip Landrigan <phil.landrigan@mssm.edu>, Howard Snyder <snyderh@email.chop.edu>, "CranmerJoanM@uams.edu" <CranmerJoanM@uams.edu>, Amy Itecsu <itecsca@UCMAIL.UC.EDU>, Richard Jackson <dickjackson@ucla.edu>, "Terry Collins" <tc1u@andrew.cmu.edu>, "deborah_cory-slechta@urmc.rochester.edu" <deborah_cory-slechta@urmc.rochester.edu>, "BLanphear@sfu.ca" <BLanphear@sfu.ca>, "dozonoff@bu.edu" <dozonoff@bu.edu>, Ted Schettler <tschettler@igc.org>, Bernard Weiss <bernard_weiss@urmc.rochester.edu>, "carl-gustaf.bornehag@kau.se" <carl-gustaf.bornehag@kau.se>, Russ Hauser <RHAUSER@hohp.harvard.edu>, Sheldon Krimsy <sheldon.krimsky@tufts.edu>, Peter Orris <porris@uic.edu>, "barbara.demeneix@mnhn.fr" <barbara.demeneix@mnhn.fr>, "Tracey.Woodruff@ucsf.edu" <Tracey.Woodruff@ucsf.edu>, Joseph Allen <jgallen@hsph.harvard.edu>, Michael Antoniou <michael.antoniou@kcl.ac.uk>, Peter DeFur <environsc@gmail.com>, "tyrone@berkeley.edu" <tyrone@berkeley.edu>, "pathunt@wsu.edu" <pathunt@wsu.edu>, Harvey Karp <dr.karp@thehappiestbaby.com>, Andreas Kortenkamp <andreas.kortenkamp@brunel.ac.uk>, "gprins@uic.edu" <gprins@uic.edu>, "rsargis@uic.edu" <rsargis@uic.edu>, "stahlhuotr@missouri.edu" <stahlhuotr@missouri.edu>, Shanna Swan <shanna.swan@mssm.edu>, "Prof. Fred vom Saal" <vomsaalF@missouri.edu>, "leonardo.trasande@nyumc.org" <leonardo.trasande@nyumc.org>, Laura Vandenberg <lvandenberg@schoolph.umass.edu>, "tzoeller@bio.umass.edu" <tzoeller@bio.umass.edu>, "kaleekreider@gmail.com" <kaleekreider@gmail.com>, Sarah Vogel <sar.vogel@gmail.com>, Frank Arthur von Hippel <Frank.vonHippel@nau.edu>, David Michaels <drdavidmichaels@gmail.com>, Emily Copeland <emily@sciencecom.org>, Gabriela Silvani Antonelli <gabriela@sciencecom.org>
Sent: 8/7/2017 10:16:30 AM
Subject: Re: Good news!

Thanks all!

As Phil Landrigan pointed out, this IS an amazing list of past recipients. And the other recipient this year is Bob Inglis, former Republican member of Congress from South Carolina who got Tea-Partied in his primary because he was trying to do the right thing on climate. I must admit that, with Inglis as an exception, the selection criteria seem to have diminished since the early years (except for Pete and Toshi Seeger) not unlike the decline in sperm count over the same period. That observed, Im not about to not accept the honor. It is truly humbling.

Thanks for all your help is making the work we do together matter.

Pete
On Aug 7, 2017, at 12:09 PM, Bruce Blumberg <blumberg@uci.edu> wrote:

Many congratulations for a well-deserved recognition, Pete!

Bruce

On 8/7/2017 6:59 AM, Amy Kostant wrote:

Dear All,

I’m delighted to tell you that the Sierra Club is honoring Pete this fall with their Distinguished Service Award (established in 1971). Below is a list of past recipients. As always, Petes in great company.

Best wishes,

Amy

Distinguished Service Award
Honors persons in public service for strong and consistent commitment to conservation over a considerable period of time. Up to three may be awarded annually.

1976  Phillip Hart
1977  Charles Warren
     Nathaniel Reed
     Edmund Muskie
1978  Thomas R. Berger
     Phillip Burton
1979  Evelyn Murphy
     Cecil Andrus
     Teno Roncalio
1980  John Cavanaugh
1981  Marian Edey
     Bob Eckhardt
     Horace Albright
     Ted Hallocik
     Nancy Fadeley
     Frank Church
     Warren Magnuson
     Gaylord Nelson
1982  Thomas H. Kimball
     Tom McCall
1983  Huey Johnson
Don Bonker
Henry Reuss
1985    Harry Hughes
Les AuCoin
1986    Barbara Eastman
1991    Margaret Ownings
Kristin Berry
1992    Peter J. Kostmayer
1994    Arthur Ravenel, Jr.
Gerry Studds
1995    John Chafee
1996    Pete & Toshi Seeger
1997    Donald Reeser
1998    Tayloe Murphy, Jr.
2003    Ross Anderson
Benjamin Brumberg
2004    Peter Douglas
Byron Sher
2005    Kevin Frey
2006    Ralph R. White, Jr.
2009    John P. Debo
Ward B. Stone
2010    Norm Dicks
2011    Keith Ellison
2013    Maxine S. Goad
2014    John Yarmuth
Robert Sweeney
2015    Mary Mushinsky
Dalton McGuinty
2016    Lois Capps
Dr. Katherine Hayhoe

Amy Kostant
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--

Bruce Blumberg, PhD.
Professor of Developmental and Cell Biology
Professor of Pharmaceutical Sciences
2011 Biological Sciences 3
University of California
Irvine, CA 92697-2300

office: 949-824-8573
lab: 949-824-6873
fax: 949-824-4709
e-mail: blumberg@uci.edu
web: http://blumberg-lab.bio.uci.edu/
     http://blumberg.bio.uci.edu/
access code not working

Pete Myers, from a mobile phone

On Jul 14, 2017, at 10:05 AM, jerry heindel <jerryheindel@gmail.com> wrote:

605 475 2875  41  #

Sent from Mail for Windows 10

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From: jerry heindel
Sent: Sunday, July 9, 2017 5:42 AM
To: Bruce Blumberg; R. Thomas Zoeller
Cc: Fred Vomsaal; Hunt, Pat; Pete Myers; Amy Kostant; Joe DiGangi
Subject: RE: December EDC meeting: response needed

So who from Europe should we invite just in case they can come.

Sent from Mail for Windows 10

---

From: Bruce Blumberg
Sent: Saturday, July 8, 2017 9:37 PM
To: R. Thomas Zoeller; jerry heindel
Cc: Fred Vomsaal; Hunt, Pat; Pete Myers; Amy Kostant; Joe DiGangi
Subject: Re: December EDC meeting: response needed

Hi everyone,

I like Tom's suggestions and additions. I feel about the same with respect to the failure of Regulatory Toxicology to integrate real science, but am growing more confident that grass roots efforts will reduce the impact of poor regulatory judgement over time. But we shall see....

To the meeting list, I might add Martyn Smith. I don't see a good reason to exclude people from other countries who may have budgets available that allow them to attend this important meeting. It could be that none of them come, but we might also be surprised.

Best,
On 7/7/2017 5:51 AM, R. Thomas Zoeller wrote:

Jerry and all. I’ve taken a stab at this by focusing first on how we might envision the organization of the meeting. With only 1.5-2.0 days, we need to be highly structured and this field defies organization. The Great Paradox to me is that the most sophisticated science in the history of mankind is ignored structurally and systematically as if there are two parallel Universes. Can these Universes be brought together? Or must one give way to the other? I have always thought that one (Regulatory Toxicology) must give way to the other (Science). But, I’m no longer confident in that. Basic Science may just come to mean new drugs to offset the adverse effects of old drugs [the very idea that we are seeing a massive opioid addiction crisis with commercials for opioid induced constipation drugs comes to mind.]

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

On Jul 7, 2017, at 7:42 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Thanks everyone. But it sure would be helpful to get more guidance on the people to invite, do we have the right ones, the best ones, do they cover all the important topics and the topics to discuss, we really need to define the list of 6-8 key topics to discuss. Then we can decide who among us will be responsible for developing each topic/session.

I can’t invite anyone until we have a better flushed out program. Please take another look. Also comment on the meeting introduction/goals that is key. I know everyone has a day job but I really need more help for this to be successful. Just take 15 minutes to go through the attachment and add comments like you were reviewing a paper. Thanks, jerry.

Sent from Mail for Windows 10
Hi Jerry and all I agree with what Fred is saying. We can think of a lot of people, and we don't know what the response rate will be. Like over-selling airline seats. A couple of additional thoughts.

First, I'm thinking of how policy should direct research and vice versa. I think it is true that research in this field has improved in terms of refining experimental design and questions to inform policy. [note: policy here means how individual chemicals are evaluated and risk assessed. Larger questions of laws, rules and processes are larger and need to be evaluated separately]. However, I don't see that policy at either level has been terribly responsive to new research. Rather, it seems like regulatory agencies have gotten better at saying how they follow sound science without actually incorporating relevant science. It might be good to have an NGO represented (maybe TEDX can do this) to talk about the large and small questions of policy<>science interplay?

The other avenue of affecting change is through public awareness/industry awareness. There should be some discussion of this issue broadly and how we can collectively interact with industry both to help them navigate the complexity of producing safer products, but also to help them communicate truthfully.

Finally, something that Joe Laakso might help with. This article made me wonder whether this is something we could emulate. [https://www.nytimes.com/2017/07/04/opinion/putting-citizenship-back-in-congress.html?r=0]

Tom

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller
On Jul 5, 2017, at 2:56 PM, jerry heindel
<jerryheindel@gmail.com> wrote:

Hi all please look at the attachment and help me to fill in the details list of attendees to ask to attend and the list of main topics to discuss. Be sure there is expertise to cover the topics. Please respond by July 14th. Just write over the plan with your suggestions and send back.

It would be good to have a solid list of participants and draft program to send out by August 1 so people can plan. Thanks for your help. jerry

Sent from Mail for Windows 10

<Eendocrine Disruption Strategies Workshop.docx>

<Eendocrine Disruption Strategies Workshop.docx>
I’m good, and very glad to see the end of 2013. I am busy writing grants and papers and excited about the stuff that’s going on. We are finally joining forces with one of the best epigeneticists (Marisa Bartolomei) to tackle our male findings.

How about you I hope the year is off to a good start.

very funny!

How are you?

p

On Jan 7, 2014, at 12:42 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hi Pete-

You have probably seen this but, if not, I think you will enjoy it. My colleague, Mick Smerden, sent the link:

I had to share what some Columbia climate scientists decided to do as a lark and is now making national news! (My son Jason is the March pin up.)

http://www.onearth.org/articles/2013/11/climatologists-turn-beefcake-for-next-years-sexiest-calendar
http://www.scientificamerican.com/article.cfm?id=climate-scientists-pose-for-pin-up-calendar

Mick

----------------------------------------
Michael J. Smerdon
Regents Professor of Biochemistry & Biophysics
Washington State University
School of Molecular Biosciences
Biotechnology Life Sciences Building
1770 Stadium Way
Pullman, WA  99164-7520
Ph: 509-335-6853
Fax: 509-335-4159
e-mail: smerdon@wsu.edu
Home page: http://www.wsu.edu/~smerdon/index.html
Thanks, Amy, I am. I am staying home. Since I will be on the phone for a good chuck of the day, there is no compelling reason to drag myself in. This way I can continue to drink huge quantities of tea.

On 1/16/15 9:10 AM, "Amy Kostant" <amy@sciencecom.org> wrote:

>Thanks Pat. I'll include this in my note. I'm pretty sure Michael's interested in cleaners/disinfectants.
> I hope you're feeling better!
>
>------Original Message------
>From: Hunt, Pat [mailto:pathunt@vetmed.wsu.edu]
>Sent: Friday, January 16, 2015 12:06 PM
>To: Laura Vandenberg; Amy Kostant; Carl-Gustaf Bornhag; Swan, Shanna
>Cc: Terry Collins; Joan Cranmer; Deborah Cory-Slechta; Peter DeFur;
>sgilbert@innd.org; Lou Guillette; Tyrone Hayes; heilig@sfms.org; Hunt,
>Patricia Ann; Dick Jackson; Landrigan, Philip; Bruce Lanphear; Pete
>Myers; hnllead@pitt.edu; porris@uic.edu; dozonoff@bu.edu; gprins@uic.edu;
>Ted Schettler; Howard Snyder; Fred vom Saal; Bernard Weiss; Tracey
>Woodruff; Tom Zoeller; Shuk-Mei Ho; stahlhutr@missouri.edu;
>blumberg@uci.edu; svogel@edf.org; Russ Hauser; leonardo.trasande@nyu.edu;
>kkreider@unfoundation.org; itescua@UCMAIL.UC.EDU;
michael.antoniou@kcl.ac.uk; sheldon.krimsky@tufts.edu;
dr.karp@thehappiestbaby.com; Emily Copeland; Gabriela Silvani
>Subject: Re: Help for a reporter
>
>I suspect that the same thing is going on in the antibacterial/disinfectant world as concerns about triclosan, triclocarbon and QACs accumulate. However, I'm not sure we can see evidence of this quite yet.
>
>On 1/16/15 9:00 AM, "Laura Vandenberg" <lvandenberg@schoolph.umass.edu> wrote:
>
>>Hi Amy,
>>
>>I don't know anything about the replacements for flame retardants in furniture, but I do know that many of the BDE flame retardants are
being replaced by tetrabromobisphenol A, or firemaster 550. These are also likely to be toxic / have endocrine disrupting properties.

Best, 
Laura

Laura N. Vandenberg, PhD
Assistant Professor
University of Massachusetts Amherst
School of Public Health & Health Sciences Department of Environmental Health Science
686 N. Pleasant Street
149B Goessmann
Amherst, MA 01003
Tel: 413.577.7405
Email:
lvandenberg@schoolph.umass.edu

From: Amy Kostant [amy@sciencecom.org]
Sent: Friday, January 16, 2015 11:57 AM
To: Carl-Gustaf Bornehag; Swan, Shanna
Cc: Terry Collins; Joan Cranmer; Deborah Cory-Slechta; Peter DeFur;
sgilbert@innd.org; Lou Guillette; Tyrone Hayes; heilig@sfms.org; Pat Hunt; Dick Jackson; Landrigan, Philip; Bruce Lanphear; Pete Myers; hlnlead@pitt.edu; porris@uic.edu; dozonoff@bu.edu; gprins@uic.edu; Ted Schettler; Howard Snyder; Fred vom Saal; Bernard Weiss; Tracey Woodruff; Tom Zoeller; Shuk-Mei Ho; stahlhut@missouri.edu; blumberg@uci.edu; svogel@edf.org; Laura Vandenberg; Russ Hauser; leonardo.trasande@nyu.edu; kkreider@unfoundation.org; itescua@UMAIL.UC.EDU; michael.antoniou@kcl.ac.uk; sheldon.krimsky@tufts.edu; dr.karp@thehappiestbaby.com; Emily Copeland; Gabriela Silvani
Subject: RE: Help for a reporter

Thanks, CG and others who have/are planning to respond. Your input is incredibly helpful.

From: Carl-Gustaf Bornehag [mailto:carl-gustaf.bornehag@kau.se]
Sent: Friday, January 16, 2015 11:56 AM
To: Swan, Shanna
Cc: Amy Kostant; Terry Collins; Joan Cranmer; Deborah Cory-Slechta; Peter DeFur; sgilbert@innd.org; Lou Guillette; Tyrone Hayes; heilig@sfms.org; Pat Hunt; Dick Jackson; Landrigan, Philip; Bruce Lanphear; Pete Myers; hlnlead@pitt.edu; porris@uic.edu; dozonoff@bu.edu; gprins@uic.edu; Ted Schettler; Howard Snyder; Fred vom Saal; Bernard Weiss; Tracey Woodruff; Tom Zoeller; Shuk-Mei Ho; stahlhut@missouri.edu; blumberg@uci.edu; svogel@edf.org; Laura Vandenberg; Russ Hauser; leonardo.trasande@nyu.edu; kkreider@unfoundation.org; itescua@UMAIL.UC.EDU; michael.antoniou@kcl.ac.uk; sheldon.krimsky@tufts.edu; dr.karp@thehappiestbaby.com; Emily Copeland; Gabriela Silvani
Agree with shanna! DEHP used as a plasticizer have been broadly
replaced by DINP. Shanna and others have showed that prenatal exposure
for DEHP is reproduction toxic for boys (e.g., shorter AGD) and we have
recently showed that DINP maybe have the same effect on baby boys
{(shorter AGD), CG
>>

Sent from my iPhone
>>

On 16 Jan 2015, at 17:48, Swan, Shanna
<<shanna.swan@mssm.edu<mailto:shanna.swan@mssm.edu>> wrote:
>>Of course DINP for DEHP
>>On Jan 16, 2015, at 10:07 AM, Amy Kostant
<<amy@sciencecom.org<mailto:amy@sciencecom.org>> wrote:
>>
>>Hi All
>>Reporter for the Chicago Tribune, Michael Hawthorne, was thinking about
>>the shift away from flame retardants in furniture which got him
>>thinking that this move away from toxic chemicals is different than
>>other product changes because they aren’t replacing one worrisome
>>compound with another. He sees that BPS is one example of how consumers
>>are exposed to replacement chemicals. He’s asked for help coming up
>>with other examples of such replacements -- currently in use or soon
>>to be in use.
>>Thanks for any suggestions
>>All best,
>>Amy
>>
>>Amy Kostant
>>Science Communication Network (SCN)
>>0: 301-654-6665
>>C: 202-255-6665
>>amy@sciencecom.org<mailto:amy@sciencecom.org>
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On 1/16/15 9:00 AM, "Laura Vandenberg" <lvandenberg@schoolph.umass.edu> wrote:

> Hi Amy,
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> I don't know anything about the replacements for flame retardants in furniture, but I do know that many of the BDE flame retardants are being replaced by tetrabromobisphenol A, or firemaster 550. These are also likely to be toxic / have endocrine disrupting properties.
> 
> Best,
> Laura
Laura N. Vandenberg, PhD
Assistant Professor
University of Massachusetts Amherst
School of Public Health & Health Sciences
Department of Environmental Health Science
686 N. Pleasant Street
149B Goessmann
Amherst, MA 01003
Tel: 413.577.7405
Email: lvandenberg@schoolph.umass.edu

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Sent: Friday, January 16, 2015 11:57 AM
To: Carl-Gustaf Bornehag; Swan, Shanna
Cc: Terry Collins; Joan Cranmer; Deborah Cory-Slechta; Peter DeFur;
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svogel@edf.org; Laura Vandenberg; Russ Hauser; leonardo.trasande@nyu.edu;
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michael.antoniou@kcl.ac.uk; sheldon.krimsky@tufts.edu;
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Subject: RE: Help for a reporter

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incredibly helpful.

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Sent: Friday, January 16, 2015 11:56 AM
To: Swan, Shanna
Cc: Amy Kostant; Terry Collins; Joan Cranmer; Deborah Cory-Slechta; Peter
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Pat Hunt; Dick Jackson; Landrigan, Philip; Bruce Lanphear; Pete Myers;
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Tom Zoeller; Shuk-Mei Ho; stahlhutr@missouri.edu; blumberg@uci.edu;
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kkreider@unfoundation.org; itescua@UCMAIL.UC.EDU;
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dr.karp@thehappiestbaby.com; Emily Copeland; Gabriela Silvani
Subject: Re: Help for a reporter
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> CG
>
> Sent from my iPhone
>
> On 16 Jan 2015, at 17:48, Swan, Shanna
> <shanna.swan@mssm.edu> wrote:
> Of course DINP for DEHP
> On Jan 16, 2015, at 10:07 AM, Amy Kostant
> <amy@sciencecom.org> wrote:
> Hi All
> Reporter for the Chicago Tribune, Michael Hawthorne, was thinking about
> the shift away from flame retardants in furniture which got him
> thinking that this move away from toxic chemicals is different than other
> product changes because they aren’t replacing one worrisome compound with
> another. He sees that BPS is one example of how consumers are exposed to
> replacement chemicals. He’s asked for help coming up with other examples
> of such replacements -- currently in use or soon to be in use.
> Thanks for any suggestions
> All best,
> Amy
>
> Amy Kostant
> Science Communication Network (SCN)
> 0: 301-654-6665
> C: 202-255-6665
> amy@sciencecom.org
Thanks, Amy. I really like putting animals in and I'm glad that you thought the tone was appropriate. I've been plagued by colleagues who want me to dial it up and colleagues who insist that I should dial it back. I just want to get it in! I've been talking to Scientific American and hoping that they will do a piece. I'm also hoping that some how we can get someone to do a large investigative piece on the FDA, but that is probably just a dream. These are appalling papers. It's especially galling those of us in academia who work so hard for our money and no that we would never get a paper like one of these published.

Thanks for your help.

Pat

---

Dear Pat,

This is a terrific letter. Very clear and to the point without sounding outright angry.

An aside, clearly to take or leave In thinking of the push back we've had to prepare for in primate studies, this may be an easy way to layout concern for animals as equally important to time, effort, dollars by adding a word:

If, indeed, the FDA and NTP have decided to move forward despite the finding that all animals are apparently exposed to an unidentified source of BPA, their joint initiative seems destined to raise more questions than it answers and to waste valuable animals, time, effort, and tax payer dollars.

Either way, this is a really nice piece.

Amy

---

Wow, Pete, I love the blog! Here's the letter to the Tox Sci editor, which pales in comparison! Amy, I've copied you on this in the hope that you will provide feedback too. As I told Pete, Tracey Woodruff and Cathi Vande Voort have agreed to sign and I am going to ask Roy Gerona too.

Pat
Send me the draft!

http://www.nano-active.com/2014/02/new-low-dose-bpa-research-in.html
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
To: Pete Myers <jpmyers@ehsic.org>, Amy Kostant <amy@sciencecom.org>
Sent: 3/3/2014 5:18:38 PM
Subject: Re: here's the blog I mentioned

Attach: [letter to tox sci - reviseddraft.docx]
Wow, Pete, I love the blog! Here's the letter to the Tox Sci editor, which pales in comparison! Amy, I've copied you on this in the hope that you will provide feedback too. As I told Pete, Tracey Woodruff and Cathi Vande Voort have agreed to sign and I am going to ask Roy Gerona too.

Pat

From: Pete Myers <jpmyers@ehsic.org>
Date: Monday, March 3, 2014 3:56 PM
To: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: here's the blog I mentioned

Send me the draft!

http://www.nano-active.com/2014/02/new-low-dose-bpa-research-in.html
We are writing in response to the recent paper on bisphenol a (BPA) by Delclos and colleagues and the related paper by Churchwell et al. These manuscripts represent the first data from an important multi-investigator initiative sponsored jointly by the National Toxicology Program (NTP), a division of the National Institutes of Health, and the U.S. Food and Drug Administration (FDA). This joint initiative to study the health effects of BPA is a costly but critically important investment that will underpin future decisions to protect the public’s health. While we applaud both federal agencies for their investment, these first publications raise serious concerns about whether meaningful data will result from this effort.

Delclos et al report the results of an extensive preliminary study designed to characterize the dose response for adverse effects induced over a wide range of BPA doses. A subsequent large-scale, multi-investigator study involving many of our highly respected colleagues will determine which endpoints are the most sensitive. The results published by Delclos et al and Churchwell et al, however, raise serious concerns about the wisdom of investing research resources and expertise in this multi-investigator initiative. In the preliminary studies reported by Delclos et al and Churchwell et al, a concerted effort was made to control for BPA contamination in both animal contact and sample collection and analysis materials. Nevertheless, serum analyses revealed that both sets of control animals (naïve and vehicle only controls) had experienced significant BPA exposure, with serum levels equivalent to those in the lowest BPA dose groups. Positive and negative controls are essential for this study: positive controls demonstrate that the animals are estrogen sensitive, and negative controls provide a point of reference for assessing adverse effects. Contamination in negative controls renders this control group useless.

Delclos et al report that adverse effects for a wide variety of endpoints were only observed at the highest BPA doses. We find this conclusion remarkable since, in the absence of uncontaminated controls, it is impossible to determine if lower doses induced effects. Churchwell et al state that the source of the contaminating BPA could not be identified, “but interpretation of the toxicological effects, observed only at the highest BPA doses, was not compromised.” This statement is astounding for two reasons. First, finding the source of the contamination and eliminating it is essential prior to conducting the planned large multi-investigator study but, unfortunately, it is our understanding that this study is already underway. If, indeed, the FDA and NTP have decided to move forward despite the finding that all animals are apparently exposed to an unidentified source of BPA, their joint initiative seems destined to raise more questions than it answers and to waste valuable time, effort, and tax payer dollars. Second, the authors’ assertion that BPA contamination at levels equivalent to that of the lowest level exposure groups has not compromised the ability of the study to detect toxicological effects is mystifying. Essentially, the authors are arguing that they can make meaningful interpretations in the absence of controls. This position is especially problematic in view of the data from numerous studies showing non-monotonic responses for a variety of BPA-induced effects. In short, we consider it both remarkable and distressing that, despite the contamination problem, the authors consider their data not only
publishable but meaningful. Further, it is discouraging that the journal’s review process not only allowed Delclos and colleagues to publish the data, but to do so without declaring the contamination problem at the outset. As written, one has to read through all of the data presented (19 journal pages in total) before the contamination issue is mentioned, since it is only acknowledged in the discussion.

Given the concerns in this field and the controversy already surrounding BPA, it is essential that researchers, reviewers, and editors maintain stringent standards. This is, however, particularly important for large-scale studies conducted using GLP guidelines, since these studies are generally accorded more weight in the regulatory arena. The studies by Delclos et al and Churchwell et al are particularly disappointing because they were conducted under the auspices of the FDA and will therefore – despite their significant limitations – be cited extensively. More importantly, the results reported in these manuscripts raise a very real concern: If the contamination problem has not or cannot be resolved, the subsequent large consortium effort seems destined to be merely another flawed study, albeit on an unprecedentedly grand scale. We fervently hope that this does not prove to be the case.
Well... the LAX to Seattle connection was just cancelled, which means we miss our flight to Pullman which is the last one tonight. I'm on the phone with Alaska Air right now. There is a flight to Spokane that would get us there at 8:44 pm. We could arrive on your doorstep tomorrow morning. Our flight out tomorrow to Seattle is at 3:35.

I've never experienced as much hay-wired dysfunction as this.

I'll let you know what happens. Really sorry about dinner!

-----"Hunt, Pat" <pathunt@vetmed.wsu.edu> wrote: -----
To: "JPMyers@ehsic.org" <JPMyers@ehsic.org>
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
Date: 12/07/2015 11:57AM
Subject: Re: Hi Pat

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   Pat
From: Pete Myers <jpmyers@ehsic.org>  
Date: Sunday, December 6, 2015 at 9:36 PM  
To: patricia hunt <pathunt@vetmed.wsu.edu>  
Subject: Re: Hi Pat

We had some glitches in our travel schedule today so didn't reach Portland yet. We'll be by tomorrow evening for sure. Probably not driving. As soon as I know what's happening I'll let you know. We will get rooms in Moscow for tomorrow night. And unless something unexpected happens we should be there for dinner.

Best,
Pete

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To: Pete Myers <jpmyers@ehsic.org>  
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>  
Date: 11/30/2015 01:39PM  
Subject: Re: Hi Pat

Hi Pete-

I’m sorry I missed your call, we went to Portland for the holiday.

Yes, the 7th/8th still works. It is a long drive from Portland but there are some very interesting parts. I doubt that you will get here too early in the afternoon, but we should definitely plan to have dinner. It might be easier and more relaxing for the two of you to have dinner at my house. Neither Pullman or Moscow is known for fine dining and I do enjoy cooking - although I would need to know about dietary restrictions for both of you. Alternatively, you may wish to extend your trip by taking advantage of good restaurants and fine wine along the way (e.g., Walla Walla), and that is fine too.

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It will be fun to see you. We have been having really cold weather but, of course, anything is possible!

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> in decades. And I haven’t been in eastern Washington since 1972.
Awesome! I like the idea of dinner cooked by Pat Hunt! Dietary requirements. We both are fairly eclectic but given a choice Margaret goes vegetarian and I avoid cheese. I'm fine with vegetarian. She loves to cook too, in groups, and I've had some wonderful evenings at their house in great cook fests with Margaret, her husband and their and friends.

How far is the drive from Moscow to Pullman?

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> in decades. And I haven’t been in eastern Washington since 1972.
Great to hear from you! And also that you're still interest. And I really value your messaging skills, as you know!

I'm happy to say that we now have a new partner in this, IIER.ch, an international economics think tank with offices in Zurich, London and Stanford. They have extremely relevant and complementary skills! And I think I mentioned before that Paul and Anne Ehrlich are on board, too.

We'll be organizing the trip over the next week or so and will check in again with possible dates as quickly as possible.

> On Oct 26, 2015, at 3:16 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:
> Hi Pete-
> I am not scared off in the least, merely busy trying to put together a proposal for a board meeting next week. I wanted to read through it one more time before composing my thoughts to you. I will try to do that today or tomorrow. I don't have major concerns but I do have some thoughts on clearer messaging, etc.
> December would be great, if you are headed this way. I am in a remote corner, but easily accessible from Seattle. I have meetings all through November, but the month of December is clear.
> With warm regards,
> Pat

> On 10/26/15, 11:48 AM, "Pete Myers" <jpmyers@ehsic.org> wrote:
>> How are you? Haven't heard back since I sent around that planning document. Did it scare you off?
>> If not, are you visitable in early December? We'd like to sit down and talk with you about the effort. The document continues to evolve as we
get valuable input from readers.

Best,

Pete
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Pat

On 11/29/15, 1:01 PM, "Pete Myers" <jpmyers@ehsic.org> wrote:

>We are still expecting to be in Pullman for the night of 7 December, if >that still works for you. This may sound crazy but we're going to drive >from Portland so that Margaret gets to see the country. Weather looks >passable. We will then fly to Seattle from Pullman on the 8th to meet >with David Montgomery (Dirt!) at UW on the morning of the 9th. Then to >SF for a next round of meetings with the Ehrlichs and their colleagues. > >We will leave Portland after sunrise on the 7th and if weather holds will
stop in a few places. We can be there by early afternoon. But don’t have to be if that’s not suitable for you. We’d love to take you and Terry for dinner. We also have time the next day. But don’t want to impose too much on you.

I’ve attached the most recent version of the Fan and also a one page summary.

Logistics: Can you recommend a hotel in Pullman that would have rooms that, hopefully, are not heavily scented?

Tell me if driving is crazy. I haven’t been up the Columbia River gorge in decades. And I haven’t been in eastern Washington since 1972.
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
To: Margaret Bergen <margaret.bergen@panswiss.org>, ITFS <jpmyers@ehsic.org>
Sent: 10/27/2015 9:08:22 AM
Subject: Re: Hi Pat

HI Margaret and Pete-

Good to hear that you are working on changes - I am anxious to see the revised version. I've pasted my global comments below in the hope that they may be of help as you revise:

The original version seemed massively overwritten to me and I kept getting mired in the heavy verbiage. I think the message needs to be streamlined so it is clear and easily accessible. I also thought there was too much focus on the problem and not enough emphasis on the goals of the project. Much of the upfront stuff seems unnecessarily long. The concerns should be obvious (although not the scale) to anyone who is inclined to join this initiative. The innovative and positive aspects of the initiative are what really MUST come out clearly in the document to get folks on board.

I look forward to seeing the revision and both of you - if that works out.

With warm regards,

Pat

---

From: Margaret Bergen <margaret.bergen@panswiss.org>
Date: Tuesday, October 27, 2015 at 3:30 AM
To: Pete Myers <jpmyers@ehsic.org>
Cc: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: Re: Hi Pat

Pat! I am so happy you are willing to take some time and look at the Fan. However, if I may please ask you to hold making corrections because we have received a couple of quite valuable comments and are folding them in right now so I would much rather you take a closer look at the new version. We will send it over to you as soon as possible!

( Sorry for not having said hello earlier -- time flies so fast and I just realized it has been almost 6 months since we last spoke in Copenhagen. ) Hope all is well.

I am really excited to be able to talk to you some more -- hopefully soon.

Hugs,

Margaret
On Oct 26, 2015, at 8:23 PM, Pete Myers <jpmyers@ehsic.org> wrote:

Great to hear from you! And also that you’re still interest. And I really value your messaging skills, as you know!

I’m happy to say that we now have a new partner in this, IIER.ch, an international economics think tank with offices in Zurich, London and Stanford. They have extremely relevant and complementary skills! And I think I mentioned before that Paul and Anne Ehrlich are on board, too.

We'll be organizing the trip over the next week or so and will check in again with possible dates as quickly as possible.

On Oct 26, 2015, at 3:16 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hi Pete-

I'm not scared off in the least, merely busy trying to put together a proposal for a board meeting next week. I wanted to read through it one more time before composing my thoughts to you. I will try to do that today or tomorrow. I dont have major concerns but I do have some thoughts on clearer messaging, etc.

December would be great, if you are headed this way. I am in a remote corner, but easily accessible from Seattle. I have meetings all through November, but the month of December is clear.

With warm regards,

Pat

On 10/26/15, 11:48 AM, "Pete Myers" <jpmyers@ehsic.org> wrote:
How are you? Haven't heard back since I sent around that planning document. Did it scare you off?

If not, are you visitable in early December? We'd like to sit down and talk with you about the effort. The document continues to evolve as we get valuable input from readers.

Best,

Pete
Hi Pete-

I'm not scared off in the least, merely busy trying to put together a proposal for a board meeting next week. I wanted to read through it one more time before composing my thoughts to you. I will try to do that today or tomorrow. I don't have major concerns but I do have some thoughts on clearer messaging, etc.

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>
> Best,
>
Pete
Yes, it would. But the question is not how many people come, its who comes and why. A small group of people focused on strategic planning is much more valuable than a larger group interested in another traditional share data scientific meeting.

On Jun 4, 2017, at 6:43 AM, Padmanabhan, Vasantha <vasantha@med.umich.edu> wrote:

Having in close to another meeting will have better attendance

Sent from my iPhone

On Jun 4, 2017, at 6:32 AM, Braun, Joseph <joseph_braun_1@brown.edu> wrote:

Jerry,

I like this idea, but think you need to tie it to an existing meeting or it will become another in an already long list of meetings related to EDCs/DOHaD (PPTOX, GRC, Copenhagen) or substantive topics (ISEE, ENDO, ASRM, etc.).

I like Vasantha's proposal for 5-minute talks that are geared towards getting feedback for new ideas. I would expand on this and give junior investigators opportunities to present their ideas for projects. I have done this at another workshop where we have 10-15 pre- or postdocs present their current work or proposed work in a very friendly environment where they receive constructive feedback. Sometimes, we invite them to return another year to hear how they progressed.

I also think it would be worthwhile to consider ways to get investigators who do animal and epidemiological work to come together and find interdisciplinary projects
they could work on. We might draw on other funded center programs to figure out what works well (e.g., Children's Centers).

I would likely attend if it were tied to another meeting, even if there weren't funds.

Joe

On Sat, Jun 3, 2017 at 9:40 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Hi all, I am writing to you as leaders in the EDC field. Please see the propose the idea of a yearly workshop to help integrate the various parts of the field and to stimulate collaborations, coordination and planning.

At this point I ask you to please respond to this email quickly, and to answer five questions.

I. Do you support this idea in general and specifically for this to get started?

II. Do you have suggestions for the workshop program/design/focus?

III. Would you attend, knowing there are no supporting funds?

IV. Would you suggest others who should attend?

V. Would you be willing to help plan the workshop?

If we are to do this we need to move quickly so please respond and within a week I can either start planning or move on to another idea! Thanks, jerry

Sent from Mail for Windows 10
Joseph M. Braun, MSPH, PhD
RGSS Assistant Professor of Public Health
Assistant Professor of Epidemiology
Epidemiology Master's Program Director
Brown University School of Public Health
Box G-S121-2, Providence, RI 02912, USA
Tel: +1 (401) 863-5397
Fax: +1 (401) 863-3713
joseph_braun_1@brown.edu
http://publichealth.brown.edu
http://brown.edu/academics/public-health/epidemiology/

******************************************************
Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues
Jerrys suggestion is different from another meeting to present data. Its a meeting to strategize where to go next. There should be very few talks. None long.

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Sent from Mail for Windows 10
From: "Hunt, Pat" <pathunt@vetmed.wsu.edu>
To: ESC <environsc@gmail.com>, Pete Myers <jpmyers@ehsic.org>
CC: "Karp, Harvey" <dr.karp@thehappiestbaby.com>, "Prins, Gail" <gprins@uic.edu>, "Lanphear, Bruce" <blanphear@sfu.ca>, "Cranmer, Joan" <cranmerJoanM@uams.edu>, "Cory-Slechta, Deborah" <deborah_cory-slechta@urmc.rochester.edu>, Peter Orris <porris@uic.edu>, "Prof. Fred vom Saal" <vomsaalf@missouri.edu>, Terry Collins <tc1u@andrew.cmu.edu>, Howard Snyder <snyderh@email.chop.edu>, "Ho, Shuk-mei" <shuk-mei.ho@uc.edu>, "Zoeller, Tom" <tzoeller@bio.umass.edu>, Ted Schettler <tschettler@igc.org>, "Ozonoff, David" <dozonoff@bu.edu>, "Hayes, Tyrone" <tyrone@berkeley.edu>, "Woodruff, Tracey" <WoodruffT@obgyn.ucsf.edu>, "Dr. Steve Heilig" <heilig@sfms.org>, "Stahlhut, Richard" <richard_stahlhut@urmc.rochester.edu>, Sheldon Krimsky <sheldon.krimsky@tufts.edu>, Philip Landrigan <phil.landrigan@mssm.edu>, "Hunt, Patricia Ann" <pathunt@wsu.edu>, Shanna Swan <shanna.swan@mssm.edu>, "Hauser, Russ" <rhauser@hohp.harvard.edu>, Amy Kostant <amy@sciencecom.org>, Bernard Weiss <Bernard_Weiss@urmc.rochester.edu>, Kalee Kreider <kaleekreider@gmail.com>, Laura Vandenberg <lvandenberg@schoolph.umass.edu>, Carl-Gustaf Bornehag <caguborn@kau.se>, Steve Gilbert <sgilbert@innd.org>, Amy Itescu <itescu@UCMAIL.UC.EDU>, Leonardo Trasande <leonardo.trasande@nyu.edu>, Michael Antoniou <michael.antoniou@kcl.ac.uk>, Emily Copeland <emily@sciencecom.org>, Joseph Allen <jgallen@hsph.harvard.edu>, Bruce Blumberg <blumberg@uci.edu>

Sent: 4/21/2017 6:56:12 PM
Subject: Re: interesting essay on science communication

Attach: [EMB4_IMG_0037[5].png]
Ill be there.

From: ESC <environsc@gmail.com>
Date: Friday, April 21, 2017 at 5:21 PM
To: Pete Myers <jpmyers@ehsic.org>
CC: "Karp, Harvey" <dr.karp@thehappiestbaby.com>, "Prins, Gail" <gprins@uic.edu>, "Lanphear, Bruce" <blanphear@sfu.ca>, "Cranmer, Joan" <cranmerJoanM@uams.edu>, "Cory-Slechta, Deborah" <deborah_cory-slechta@urmc.rochester.edu>, Peter Orris <porris@uic.edu>, Fred Vom Saal <vomsaalf@missouri.edu>, Terry Collins <tc1u@andrew.cmu.edu>, Howard Snyder <snyderh@email.chop.edu>, "Ho, Shuk-mei" <shuk-mei.ho@uc.edu>, "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, Ted Schettler <tschettler@igc.org>, "Ozonoff, David" <dozonoff@bu.edu>, "Hayes, Tyrone" <tyrone@berkeley.edu>, "Woodruff, Tracey" <WoodruffT@obgyn.ucsf.edu>, "Dr. Steve Heilig" <heilig@sfms.org>, "Stahlhut, Richard" <richard_stahlhut@urmc.rochester.edu>, Sheldon Krimsky <sheldon.krimsky@tufts.edu>, Philip Landrigan <phil.landrigan@mssm.edu>, "Hunt, Patricia Ann" <pathunt@wsu.edu>, Shanna Swan <shanna.swan@mssm.edu>, "Hauser, Russ" <rhauser@hohp.harvard.edu>, Amy Kostant <amy@sciencecom.org>, Bernard Weiss <Bernard_Weiss@urmc.rochester.edu>, Kalee Kreider <kaleekreider@gmail.com>, Laura Vandenberg <lvandenberg@schoolph.umass.edu>, Carl-Gustaf Bornehag <caguborn@kau.se>, Steve Gilbert <sgilbert@innd.org>, Amy Itescu <itescu@UCMAIL.UC.EDU>, Leonardo Trasande <leonardo.trasande@nyu.edu>, Michael Antoniou <michael.antoniou@kcl.ac.uk>, Emily Copeland <emily@sciencecom.org>, Joseph Allen <jgallen@hsph.harvard.edu>, Bruce Blumberg <blumberg@uci.edu>

Subject: Re: interesting essay on science communication
Tomorrow we March!

Sent from my iPhone

On Apr 21, 2017, at 3:42 PM, Pete Myers <jpmyers@ehsic.org> wrote:

from Slate

http://slate.me/2pMzxrS
HELP CURE
MALIGNANT NARCISSISM
Fund SCIENCE
I asked her about electronic receipts, specifically citing Apple. She said that while this approach may work for the part of the economic spectrum it will leave out a lot of people.

> On Jun 26, 2015, at 12:31 PM, Bruce Lanphear <bpl3@sfu.ca> wrote:
> Pete:
> What about emphasizing the use of electronic receipts?
> I can't use it in Vancouver, but I think the iPhone allows the retailer to send the buyer an electronic receipts instead of a paper receipt.
> Will we need paper receipts in 5 years?
> Cheers,
> Bruce
> ----- Original Message -----
> From: "Pete Myers" <jpmyers@ehsic.org>
> To: "Harvey Karp" <dr.karp@thehappiestbaby.com>, "Gail Prins"
> <gpri<@uic.edu>, "Bruce Lanphear" <blanphear@sfu.ca>, "Joan Cranmer"
> <cranmerJoanM@uams.edu>, "Deborah Cory-Slechta"
> <deborah_cory-slechta@urmc.rochester.edu>, "Peter Orris" <porris@uic.edu>,
> "Prof. Fred vom Saal" <vomsaalf@missouri.edu>, "Terry Collins"
> <tclu@andrew.cmu.edu>, "Howard Snyder" <snyderh@email.chop.edu>, "Peter
> DeFur" <pldefur@igc.org>, "Shuk-mei Ho" <shuk-mei.ho@uc.edu>, "Tom Zoeller"
> <tzoeller@bio.umass.edu>, "Prof. Louis J. Guillette"
> <lou.guillette@gmail.com>, "Ted Schettler" <tschettler@igc.org>, "David
> Ozonoff" <dozonoff@bu.edu>, "Tyrone Hayes" <tyrone@berkeley.edu>, "Tracey
> Woodruff" <WoodruffT@obgyn.ucsf.edu>, "Dr. Steve Heilig" <heilig@sfms.org>,
> "Richard Stahlhut" <richard_stahlhut@urmc.rochester.edu>, "Sheldon Krimsky"
> <sheldon.krimsky@tufts.edu>, "Philip Landrigan"<phil.landrigan@mssm.edu>,
> "Pat Hunt" <pathunt@wsu.edu>, "Shanna Swan" <shanna.swan@mssm.edu>, "Russ
> Hauser" <rhauser@hohp.harvard.edu>, "Bruce Blumberg" <blumberg@uci.edu>,
> "Amy Kostant" <amy@sciencecom.org>, "Bernard Weiss"
> <Bernard_Weiss@urmc.rochester.edu>, "Kalee Kreider"
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> <lvandenberg@schoolph.umass.edu>, "Emily Copeland" <emily@sciencecom.org>,
> "Carl-Gustaf Bornehag" <caguborn@kau.se>, "Michael Antoniou"
> <michael.antoniou@kcl.ac.uk>, "Steve Gilbert" <sgilbert@innd.org>, "Leonardo
> Trasande" <leonardo.trasande@nyu.edu>, "Amy Itescu" <itescua@UCMAIL.UC.EDU>
> > Sent: Friday, June 26, 2015 9:22:04 AM
> > Subject: interesting phone call
> >
> > Shira Gans is the Senior Policy Director at the NYC Department of
> Consumer Affairs NYC's consumer protection agency. Shira guides the
> agency's policy agenda using legal action, rule making, and policy reports
> to address and bring attention to a variety of consumer protection issues,
> such as BPA in receipts.
> > She called me yesterday to talk about BPA in thermal receipts. NYC is
> considering developing policies on this and wanted advice on replacements.
> The conversation meandered over a range of issues much of which
> fundamentally came down to the fact she is a history major and doesn't have
> a ready stable of scientists she can turn to for advice.
> > mmm you can see where this is going.
> > She's going to be dealing with a lot of our issues at the consumer level.
> Phthalates, triclosan, BPA, PFCs, etc.
> > Any in this group that might be willing to speak with her occasionally in
> an organized fashion say once a quarter unless there's something hot on the
> move?
His name is David Heath and he works for the DC-based Center for Public Integrity. Their investigations are co-published with places like PBS Newshour, Time, ProPublica, etc.

On Feb 25, 2015, at 6:07 PM, Pete Myers <JPMyers@ehsic.org> wrote:

absolutely!

On Feb 25, 2015, at 12:27 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

If you think my perspective would be helpful, I will talk.
probably the easiest way to handle the breakout groups is, once we know how many there are, go around the room and have people count 1 2 3 4 up to n where N is the number of groups, and then repeat until everyone has a number. there should be a minimum of say 10 people in each group.

groups are asked to answer the same questions, like the Chapel Hill process

On Aug 10, 2017, at 2:12 PM, Vomsaal, Frederick S. <VomsaalF@missouri.edu> wrote:

We would need Jerry to give a welcome opening talk that included what was going to be done. If breakout groups begin the meeting, then everyone coming should be asked ahead of time which group they would be in cant do that at the meeting as we might find that the majority of people would end up in one of the groups.

Another approach would be to divide participants into 4 groups and ask them each to provide answers to the same set of questions including what are the critical issues in the EDC field. The subsequent breakout groups could then be based on the answers provided by participants concerning what issues should be covered.

I prefer move interaction among the participants about a topic than listening to lectures.
Fred

I just want to say that I could deliver a talk with Fire and Fury like the world has never seen before!

Ok, seriously, I do think that to get the most out of this, we should develop a different kind of structure. What if:

We begin with, say, 4 breakout groups with each group operating at a different level

1. Whats the most important science to be done
2. How to address regulatory processes?
3. Linking science to legal processes
4. Linking science to consumer products?

(I just made these up)

Then, after that discussion (individual groups and plenary), break up into 4 groups where each group is composed of members of the original, to have a cross-cutting discussion.

(I just made this up too). The point really is to shake things up from the beginning. In fact, I think this topic is so big that it is hard to have an encapsulating 15 or 20 min talk.

Tom

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

On Aug 10, 2017, at 1:10 PM, Pete Myers <jpmyers@ehsic.org> wrote:

I agree with Bruce that we need to start off with a summary, but the way to get that is not to load responsibility on one person, who despite his brilliance, can’t possibly know everything, and instead use a breakout with reports back as a form of crowdsourcing. And also a strong signal that this meeting is different. It’s not about received wisdom. It’s about shared brainstorming.

On Aug 10, 2017, at 12:39 PM, Bruce Blumberg <blumberg@uci.edu> wrote:

I partly agree with Pete and partly disagree. First, I think that we need to start off with a summary of where we were/are with respect to EDC policy around the world, where we have succeeded and how we have failed; Tom is the best person to do this. His talk could be slightly shorter, though - perhaps 30 minutes. Then charge for breakout groups, break and go to first breakout session.

I agree that Kanno’s talk can be moved to a later part of the meeting, but disagree that this is an “untried idea”. Rather, labeling our field endocrine disruption is, in retrospect, one of our greatest mistakes because it limits the scope of chemical effects on biology.
We are STILL trying to convince the wider scientific community that endocrine disruption can cause cancer and various other adverse outcomes despite voluminous evidence to this effect. In contrast, virtually everyone in the scientific community, even toxicologists, agree that disrupted cellular signaling pathways cause cancer and a host of other maladies. Signaling disruptors, or signal toxicity or whatever we end up calling it is the future of our field, in my opinion and represents a long-standing, missed opportunity. Why not open this discussion at such a meeting? I think it is overdue.

I don’t know what recent decisions of Linda’s Pete is specifically referring to, although I have heard rumors. It would be a mistake to not invite Linda to our meeting, but also a mistake to feature her in a prominent role as if we are asking for her leadership. I think that Linda’s input will be valuable, but would not like her to lead or dominate any segment of the meeting, irrespective of the fact that she controls the biggest pot of money for our work.

I would lose the general discussion at 4:45 about challenges/opportunities related to risk assessment, guideline studies and AOPs and convert this into breakout groups. I would convert the two plenaries about EDC policies on Tuesday into a shorter, general discussion of no more than an hour. If we end Monday with a breakout session, then we need time for reports, either later on Monday, or earlier on Tuesday.

I also agree with Pete that we need a specific session led by Tillery on how our community can best work with trial lawyers to obviate the lack of regulatory progress on EDCs, indeed to overcome the Trumpian reversal of much that we have worked toward. Steve has definite ideas about how to accomplish this and others need to hear this from him. At the same time, I can predict that Linda (and perhaps others) will not be happy about this since lawyers are not exactly universally beloved. However, in my view, it is time to stop pussyfooting around and trying to talk nicely with industry whores such as Dietrich et al. about the merits of our science, pretending that they are reasonable people who will be persuaded by strong arguments. They are owned and will never change their position. Like big tobacco, the only message they and their sponsors will understand is current and future financial pain... Engaging with the legal community to bring this pain to industry based on strong science, coupled with grass roots efforts to have the public demand the withdrawal of toxic chemicals from use is the surest way to accomplish our goals, irrespective of how little action there is in the regulatory sphere and how much money industry throws at manufacturing doubt.

Best,

Bruce

I also

On 8/10/2017 5:07 AM, Pete Myers wrote:

this new agenda is a big step backwards. I have commented on it in the attached document.
On Aug 10, 2017, at 6:51 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Remember we meet tomorrow at 1pm 605 475 2875

I tried to take everyones comments into account for this new draft

Please have draft pulled up so we can go over it step by step and try to finalize most of it. Thanks, jerry

Sent from Mail for Windows 10

<8 10 17Endocrine Disruption Strategies Workshop v5. docx.docx>

--

Bruce Blumberg, PhD.
Professor of Developmental and Cell Biology
Professor of Pharmaceutical Sciences
2011 Biological Sciences 3
University of California
Irvine, CA  92697-2300

office: 949-824-8573
lab: 949-824-6873
fax: 949-824-4709
e-mail: blumberg@uci.edu
web: http://blumberg-lab.bio.uci.edu/
     http://blumberg.bio.uci.edu/
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Please have draft pulled up so we can go over it step by step and try to finalize most of it. Thanks, jerry
Sent from Mail for Windows 10

<8 10 17Endocrine Disruption Strategies Workshop v5. docx.docx>

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Bruce Blumberg, PhD.
Professor of Developmental and Cell Biology
Professor of Pharmaceutical Sciences
2011 Biological Sciences 3
University of California
Irvine, CA 92697-2300

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lab: 949-824-6873
fax: 949-824-4709
e-mail: blumberg@uci.edu
web: http://blumberg-lab.bio.uci.edu/
http://blumberg.bio.uci.edu/
From: Pete Myers <jpmyers@ehsic.org>
To: Jerry Heindel <jerryheindel@gmail.com>
CC: Bruce Blumberg <blumberg@uci.edu>, Amy Kostant <amy@sciencecom.org>, "Hunt, Pat" <pathunt@vetmed.wsu.edu>, "Prof. Fred vom Saal" <VomsaalF@missouri.edu>, "R. Thomas Zoeller" <tzoeller@Bio.umass.edu>
Sent: 8/10/2017 5:07:47 AM
Subject: Re: jerry latest draft for discussion tomorrow

Attach: [2017-0810 Endocrine Disruption Strategies Workshop v5. docx.docx]
this new agenda is a big step backwards. I have commented on it in the attached document.

On Aug 10, 2017, at 6:51 AM, jerry heindel <jerryheindel@gmail.com> wrote:

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Introduction/Goal:

The EDC topic is particularly challenging because it cuts across many disciplines from molecular physiology and endocrinology to genetics and personalized medicine, evolution and population ecology and economics and sociology. Studies of EDCs have and will continue to provide key data that can improve human and environmental health but the impact on health will only be as successful as we are at communicating the findings and implications to clinicians, the general public as well as chemists, lawyers, regulators and policy makers. Many people and working groups have become interested in the effects of EDCs including but not limited to the important work of SCN and EHN, CHE, TEDX, EDCfree and others in the NGO community, the Endocrine Society, ACOG and FIGO and many more around the globe. The study of EDCs has required that new biological insights are identified in parallel with work on chemical effects in a number of different fields. We propose that the EDC field as a whole, including scientific understanding and its impact on disease burden could be strengthened by the development of a yearly Forum that increases communication and collaboration across disciplines.

The goal of this workshop is to help identify strategic needs and opportunities to advance the field and encourages strategic collaborations. This forum will provide a platform to define the critical issues facing the field, and develop plans to improve knowledge sharing, coordination and collaboration that will reduce the impact of EDC exposures on human health, continue to build demand for safer chemicals, help chemists respond to that demand and improve the impact of EDC science on the regulation of EDCs. A result of this workshop will be the development of a yearly EDC Forum to continue the work started at this first workshop.

The initial meeting, to be held in Raleigh/Durham 4-5 December 2017, will focus on key areas important to the EDC field. The focus will be refined and sharpened over the coming months, but might include, efforts to bolster consumer interest in safer products, collaboration with chemists on chemical design, identify research needs and opportunities, improved coordination/collaboration among NGOs and regulatory and policy needs and coordination with lawyers around opportunities to foster change through litigation. There are specific needs in the EU centered around EDC regulations/guidelines and in the US centered around the Administration’s focus on undermining environmental policies and the emergence of science deniers. The field also needs to build/strengthen ties between medical professional groups whose health goals are impaired by EDCs.

Planning Committee: Jerry Heindel, Pete Myers, Amy Kostant, Fred vom Saal, Bruce Blumberg, Tom Zoeller, Pat Hunt, Joe DiGangi
Draft Program (still under construction)

Sunday evening, reception at Jerry Heindel’s House

Monday, December 4th Focus on Science

8:30 Welcome, introduction

8:45 Overview of Meeting

9:00 Plenary: Tom Zoeller, Significant impacts of EDC research on human health: assumptions, data gaps and lessons learned

9:40 General Discussion

10:15 Break

10:40 Plenary: Jun Kanno, What’s in a name: Signal toxicity, obesogen, metabolism disruptors

11:15 Discussion

11:30 General Discussion: EDC research needs to improve impact of research, new approaches/new technologies...are we asking the right questions? Leaders: Leo Trasande, Bruce Blumberg, Linda Birnbaum

12:30 Lunch

1:45 Breakout Groups, Focus Question (3 with mixed expertise): What are the big health challenges that have not yet been examined through an EDC lens and how might that happen? What are the next issues that needs to be developed? Group Leaders: Gail Prins, Russ Hauser, John McLachlan

3:15 Break

3:45 Breakout Group Report

4:45 General Discussion: Challenges/opportunities related to risk assessment, guideline studies and AOPs, Leaders: Shirlee Tan, ?????

6:00 End for day...

Dinner at Hotel or restaurant at Crabtree Mall, (0.5 miles)

Tuesday December 5th Focus on Policy, Outreach and Communication

8:30 Plenary: EDC policies in the EU: What is our role? (Barbara Demeniex)

9:15 Plenary: EDC policies in the US: What is our role? (Ken Cook)

10:00 Break

10:30 Breakout Groups, Focus Question: (3 with mixed expertise): How do we improve the knowledge and acceptance of EDC data/principles/effects on human and wildlife health? Group Leaders: Jane Muncke, Sally Darney, Jodi Flaws

Commented [JPM1]: I think this is a giant step backward. First, it puts too much of a burden on Tom. Second it loses the opportunity to gain from the wisdom of all the smart people in the room. Break out groups are a much better way to go. We’re much more likely to get input from people in them than in a single room that begins with a 40 minute lecture.

If you have 4 (example) break out groups, immediately you have 4 times as many people speaking simultaneously, because in one large group only one person gets to talk at once. Further, many people are inhibited by large groups. So in one large group you censor a lot of thinking from shy but just as knowledgeable people.

Beginning the meeting with a lecture is a signal that this meeting is more business as usual. This is not offered as a criticism of Tom AT ALL. If we structure this to be a standard scientific meeting with wisdom on high, then we miss real opportunities to learn from the assembled group.

Commented [JPM2]: This is too un-tried an idea to feature so prominently in the meeting. If it’s to get a plenary, then have it later. Placed here it will be highly disruptive of the other issues we must face.

Commented [JPM3]: Given her recent decisions I don’t think she should be invited. Her presence will suppress creative open thinking because people will worry that she will interfere again with grant decisions. That’s the elephant in the room. I don’t take NIEHS money so I can say it.
• What is our message?
• How do we change people’s thinking?
• Who is the message for: clinicians, basic scientists, lay community, science deniers, journalists
• How do we expand avenues of communication, webinars, social media, infographics, etc?
• What is the role of systematic reviews?
• What is the role of journals?
• What is the role of NGOs?

12:00 Breakout group reports

12:45 Lunch

1:45 General Discussion: How can we expand ties between NGOs, Scientific Societies and Medical groups, Leaders: Carol Kwaitkowski, Joe Laasko, Linda Giudice

2:30 General Discussion: How to develop a unified multinational response to attacks on scientific integrity from various sources, including building capacity to work with trial lawyers Leaders: Pete Myers, Steve Tillery, Amy Kostant

3:30 Break

4:00 Plenary Session: Moving Forward...General Discussion of next EDC Forum
• Can we develop working groups/focused workshops? Or listservs? What would be their purpose/goals?
• Plan for the next year’s meeting... Switzerland after Gordon Conference...need planning committee
• Discussion of meeting output

5:00 Workshop ends

Participants (Estimated max 40)
Jerry Heindel
Bruce Blumberg
Fred vom Saal
Pete Myers
Pat Hunt
Jodi Flaws
Russ Hauser
Leo Trasande
Gail Prins
Ana Soto
Philippe Grandjean

Commented [JPM4]: This needs to focus on how to facilitate work with trial lawyers. It should begin with comments by Tillery and then have a panel discussion with him and scientists who have worked with trial lawyers to reflect on what works and what doesn’t, and what can we do to become better at it. Alternatively, Tillery could include in his opening remarks comments about what science he needs to make the case, and then breakout groups could brainstorm on ideas to take to trial lawyers.
Linda Birnbaum
Frank von Hippel
Heather Patisaul
Linda Giudice
Laura Vandenberg
Shirlee Tan
Ken Cook
Terry Collins
Carol Kwiatkowski
Shorey Myers
Barbara Demeniex
Jane Munke
Jun Kanno
Loretta Doan
Steve Tillery
Amy Kostant
Toshi Shioda
Aly Cohen
Sharyle Patton
John McLachlan
Heather Stapleton
Joe Laasko
Veena Singla
Folami Ideraabdullah

**Awaiting Response:** If you know any of these people...help me get their attention and acceptance!

Andrea Gore
David Crews
Rob Sargis
Matt Cave
David Collier
Tim Konte
Rena Steinzor
Leah Segedie
Jeff Wise
Hi Jerry,

I'm out next week, but whenever the call is, I'll try to make it.

Amy

From: Vomsaal, Frederick S. [mailto:VomsaalF@missouri.edu]
Sent: Friday, July 28, 2017 2:56 PM
To: jerry heindel; Bruce Blumberg; "Hunt, Pat"; 'Pete Myers'; Amy Kostant; R. Thomas Zoeller
Subject: Re: jerry needs help...call missed today

I have a 10:30 (EDT) meeting so 1 PM EDT would be better for me,
Fred

From: Jerry heindel <jerryheindel@gmail.com>
Date: Friday, July 28, 2017 at 1:20 PM
To: Fred vom-saal <VomsaalF@missouri.edu>, Bruce Blumberg <blumberg@uci.edu>, "Hunt, Pat" <pathunt@vetmed.wsu.edu>, 'Pete Myers' <jpmyers@ehsic.org>, Amy Kostant <amy@sciencecom.org>, Tom Zoeller <tzoeller@Bio.umass.edu>
Subject: jerry needs help...call missed today

Somehow everyone but Fred forgot today's call to plan the December EDC Strategies meeting. I really need a call with all of you next week, there are lots of decisions to make.

Can we meet next week Tuesday or Wednesday at noon? Please let me know. I will send out updates and questions over the weekend. jerry

Sent from Mail for Windows 10
What day, Fred? I can't do Tuesday. Wednesday works.

On Jul 28, 2017, at 2:56 PM, Vomsaal, Frederick S. wrote:

I have a 10:30 (EDT) meeting so 1 PM EDT would be better for me,
Fred

Somehow everyone but Fred forgot today’s call to plan the December EDC Strategies meeting. I really need a call with all of you next week, there are lots of decisions to make.

Can we meet next week Tuesday or Wednesday at noon? Please let me know. I will send out updates and questions over the weekend. jerry
Yes. I think we'll get some interesting and widely varying responses. There will be some stuff that everyone identifies. And a bunch that has overlaps with some groups. And some outliers identified by only one.

On Aug 10, 2017, at 4:41 PM, Jerry Heindel <jerryheindel@gmail.com> wrote:

So you want the first breakout to all focus on the same topic and questions, and that topic relates to state of science

Sent from my iPad

On Aug 10, 2017, at 3:59 PM, Pete Myers <jpmyers@ehsic.org> wrote:

I think the first break out should have a simple charge common across all all groups and address the following types of questions. Note these are not nearly as specific as what Jerry is suggesting. I'm trying to encourage brainstorming.

Where has the science gone well. Why. What can we learn from it.

Where has it not gone well? Why? What can we learn from it?

Where should the science go next based on what we know now?

How many groups we have should be determined by how many people we have. There should be 10-15 people per group, randomly assigned.

Well get overlap among the groups answers and also differences. All that will be informative.

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So to emulate that we would have 5 initial breakouts. Just made these up what are the best breakouts to cover the waterfront?
For example: Each session would have experts in the areas discussed and some outsiders to stimulate discussion
What is the most important science to be done (in vitro, animal, human)
How to impact regulation (AOPS and Guidelines)
How to affect policy
How to improve communications (NGOs, community, societies, clinical)
Linking science to legal processes
OTHER IDEAS?

EACH PANEL WOULD ADDRESS THE SAME QUESTIONS as examples just made these up. What are the best questions?
Where are we?
Success stories?
Key issues to address to move forward
Assumptions, data gaps
New areas to start/build

This would take 3 hrs with a short break
Then some presentation to fill the morning
Lunch
Breakout reports

SECOND BREAKOUTS.. Now we need new breakouts with some representation from each group. The new groups would answer the same questions.

THIS IS WHERE I NEED HELP. WHAT ARE THE INTEGRATING QUESTIONS. (across experiments, regulation, policy, communications)

How do we move these areas forward?
Who are the players that need to be engaged?
What are the challenges and opportunities and gaps to fill?
What resources are needed?
OTHER IDEAS
Another presentation to fill the afternoon

Second day
All morning reports and discussion

Presentations on topics of importance but not covered in detail

Discussion on future activities to keep the momentum, improve communication and impact
Next meeting
What to do between meetings.
Meeting report.
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On Aug 10, 2017, at 2:12 PM, Vomsaal, Frederick S. <VomsaalF@missouri.edu> wrote:

We would need Jerry to give a welcome opening talk that included what was going to be done. If breakout groups begin the meeting, then everyone coming should be asked ahead of time which group they would be in cant do that at the meeting as we might find that the majority of people would end up in one of the groups.

Another approach would be to divide participants into 4 groups and ask them each to provide answers to the same set of questions including what are the critical issues in the EDC field. The subsequent breakout groups could then be based on the answers provided by participants concerning what issues should be covered.

I prefer move interaction among the participants about a topic than listening to lectures.
Fred
Subject: Re: jerry latest draft for discussion tomorrow

I just want to say that I could deliver a talk with Fire and Fury like the world has never seen before!

Ok, seriously, I do think that to get the most out of this, we should develop a different kind of structure. What if:

We begin with, say, 4 breakout groups with each group operating at a different level
  1. What's the most important science to be done
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(I just made these up)

Then, after that discussion (individual groups and plenary), break up into 4 groups where each group is composed of members of the original, to have a cross-cutting discussion.

(I just made this up too). The point really is to shake things up from the beginning. In fact, I think this topic is so big that it is hard to have an encapsulating 15 or 20 min talk.

Tom

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

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I agree with Bruce that we need to start off with a summary, but the way to get that is
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Cc: R. Thomas Zoeller; Bruce Blumberg; Jerry Heindel; Amy Kostant; Hunt, Pat
Subject: Re: jerry latest draft for discussion tomorrow

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      http://blumberg.bio.uci.edu/
Hi Jerry-

I agree with the comments of others, but have taken it one step further: I think EDCs is not a discipline per se, but a topic that crosses many disciplines. The study of EDCs has provided now biological insight in a number of different fields, but the potential effects of exposure takes these studies far beyond the realm of biology. This meeting should provide a means of reaching across disciplines to inform the science. But the impact on the health of humans and other species means that the EDC field must invent some type of structure for moving far beyond the science. Isn't that what we want from this meeting?

Pat

From: Bruce Blumberg <blumberg@uci.edu>
Date: Tuesday, July 18, 2017 at 12:36 PM
To: Pete Myers <jpmyers@ehsic.org>, Jerry Heindel <jerryheindel@gmail.com>
Cc: "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, Amy Kostant <amy@sciencecom.org>, Fred Vom Saal <vomsaalF@missouri.edu>, patricia hunt <pathunt@vetmed.wsu.edu>
Subject: Re: jerry updated workshop plan

I have added my comments to those of Tom and Pete.

Best,

Bruce

On 7/18/2017 7:57 AM, Pete Myers wrote:

comments on the agenda, attached.

On Jul 18, 2017, at 9:43 AM, jerry heindel <jerryheindel@gmail.com> wrote:

Thanks Tom, as usual you have excellent ideas. Let's see what others think. jerry
From: R. Thomas Zoeller  
Sent: Tuesday, July 18, 2017 8:42 AM  
To: jerry heindel  
Cc: Amy Kostant; Fred Vomsaal; Pete Myers; Bruce Blumberg; Hunt, Pat  
Subject: Re: jerry updated workshop plan

Here are some thoughts!

T

--

Bruce Blumberg, PhD.  
Professor of Developmental and Cell Biology  
Professor of Pharmaceutical Sciences  
2011 Biological Sciences 3  
University of California  
Irvine, CA  92697-2300  

office:  949-824-8573  
lab:  949-824-6873  
fax:  949-824-4709  
e-mail:  blumberg@uci.edu  
web:  http://blumberg-lab.bio.uci.edu/  
http://blumberg.bio.uci.edu/
Introduction/Goal:
The EDC topic is particularly challenging because it encompasses sub-topics from molecular physiology and endocrinology to genetics and personalized medicine, economics and sociology. Studies of the EDC field have shown that improving health but the impact on health will only be as successful as we are at communicating the findings and implications to the general public.

The field is extremely lucky to have many people and working groups have become interested in the effects of EDCs, including but not limited to, the important work of SCN and EHN, CHE, TEDX, EDCfree and the NGO community, the Endocrine Society and many more around the globe. Nonetheless, the study of EDCs, because it is not a discipline per se, field has no formal structure or organization, to help with planning, collaboration or coordination and outreach.

The goal of this workshop is thus to set up a permanent “structure”, a yearly brainstorming/planning session workshop to help coordinate all the ongoing activities in the EDC field. This “structure” will provide a platform to define the critical issues facing the field, and develop plans to improve knowledge sharing, coordination and collaboration that will reduce the impact of EDC exposures on human health.

The initial meeting will focus on three key areas important to the EDC field, research, outreach and communication, and regulatory and policy. The goal is to “see” where the field is, how it got there and how to move forward to improve our ability to reduce disease from environmental exposures.

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1. Significant impacts of EDCs on human health: major accomplishments/ how were they accomplished/ lessons learned
   1.a. Because "EDCs" by definition interfere with hormones, I’m wondering if this plenary can focus on those research questions that are common among all EDCs. In my experience, some EDC work actually uncovers new ways of understanding the basic endocrinology/biology whereas other kinds of studies highlight how regulators should change the way they think about things (i.e., “applied”). I’m wondering if this could be distilled across endocrine systems?

2. EDC research needs to improve impact of research/ new approaches/technologies
   2.a. 1a would lead into this more effectively?

3. Where are the new research opportunities in a changing field/future planning?
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1. Guideline studies and AOPs and EDCs
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Dinner at Hotel or restaurant at Crabtree Mall, (0.5 miles)

Tuesday December 5th

8:30 Plenary: Overview Outreach and Communication Status and Needs

9:00 Overview of goals and plans of Advocacy Groups/ NGOs and Societies

TEDX, CHE, SCN, EHN, EWG, PHRE, EDCFree, Endocrine Society (what are the main key ones to focus on here?) 15 min each

10:15 Break

10:30 Breakouts: How to improve the knowledge and acceptance of EDC data/principles/effects on human and wildlife health

1. How to Communicate with and gain acceptance of scientific data by community, clinicians, science deniers? How do we change peoples’ thinking?
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- Can we develop working groups/focused workshops? Or listservs? What would be their purpose/goals?
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Bruce Blumberg
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Tom Zoeller
Pat Hunt
Jodi Flaws
Russ Hauser
Joe DiGangi
Leo Trasande
Shanna Swan
Gail Prins
Ana Soto
Robert Sargis
Matt Cave

Commented [BB26]: This is very important because both pharma and chemical companies are asserting and promoting the idea that only they are doing "sound science".

Commented [BB27]: you need some industry people here to facilitate this, I think. This is a huge can of worms. They will pretend to cooperate and then use what they have learned from us to facilitate the next wave of attacks, as we have already seen from the Dietrich crowd after the extensive discussions between the EDC crowd and the corporate shills.

Commented [BB28]: Need grass roots groups here.....
Philippe Grandjean
Linda Birnbaum
Frank von Hippel
Heather Patisaul
Andrea Gore
David Crews
Linda Giudice
Laura Vandenberg
Susan Jobling
Juliette Legler
Andreas Kortenkamp
Ake Bergman
Angel Nadal
Tracy Woodruff
Shirlee Tan
Joe Laasko
Michael Lerner
Ken Cook
Terry Collins
Carol Kwiatkowski
Karen Wang
Jeff Wise
Shorey Myers
Barbara Demeniex
Mike Schade
John Pierre Bourguignon
Niels Skakkebaek
Arlene Blum
Ninja Reineke
Gwynne Lyons
Jane Muncke

Expertise in Regulatory and Policy: Pete Myers, Tracy Woodruff, Shirlee Tan, Heather Patisaul, Tom Zoeller, Joe Laasko, Joe DiGangi, Michael Lerner, Ken Cook, Linda Birnbaum

Expertise in Green Chemistry: Terry Collins

Expertise in Communications: Amy Kostant, Pete Myers, Carol Kwiatkowski, Tracy Woodruff, Karen Wang, Jeff Wise, Pat Hunt

NGO community/Scientific Societies: EHN, EWG, TEDX, CHE, Endocrine Society, SCN, PHRE, PEDS, Heal, Chemtrust, HEFN, community action groups, Mind the Store(safer chemicals: healthy families), Arlene Bloom, SEHN (Ted Schecter), EDF, (others?)
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Representative from EDC Gordon Conference Planning (June 2-8 Les Diablerets Switzerland): Jodi Flaws

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**Science.** What are the first best issues to address from molecular/biochemical to epidemiology. In turn, these topics can be viewed as being “new research” to “theoretical underpinning”.

- a. What significant changes/impacts have we made
- b. How did we make these changes/impacts
- c. How to improve on the processes...how do we change thinking/outcomes
- d. How do we fill data gaps to improve impact and acceptance
- e. What are the new science areas that need focus/development?

**Translation.** This is all about communication: translating the science to all the other entities (other scientists, the general public, policy makers, regulatory agencies). Translating the science needs to be goal oriented and those goals seem to be to:

- a. Improve risk assessment
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- d. Moving from outside to an insider... clinical, toxicology, OECD, policy, regulatory (EFSA, ECHA...) how to get message to broader audience... endocrine perspective
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- f. Counteract...fake science, science deniers?
- g. Communicate with and gain acceptance of scientific data by community, clinicians, regulators, policy makers, science deniers
- h. Publications, reviews, infographics needed
- i. Expansion of use of social media
- j. Need for unified multi-national response to attacks on scientific integrity...sense about science
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**Partnerships.** Two accomplish the goals laid out in 1 and 2, we need to form effective partners among those working at the different levels. What are the important domains and the actors within them. Discussion by all NGOs of their activities and planning for next year so everyone
has better idea of what is going on in the field. This could stimulate better coordination, collaborations and avoid overlap.

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Sent from Mail for Windows 10

From: R. Thomas Zoeller
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Cc: Amy Kostant; Fred Vomsaal; Pete Myers; Bruce Blumberg; Hunt, Pat
Subject: Re: jerry updated workshop plan

Here are some thoughts!

T
Endocrine Disruption Strategies Workshop  
December 4-5, 2017  
Hotel in Raleigh NC (TBD)

Introduction/Goal:

The EDC topic is particularly challenging because it encompasses sub-topics from molecular physiology and endocrinology to personalized medicine, economics and sociology. The EDC field is providing key data that can improve health but the impact on health will only be as successful as we are at communicating the findings and implications to people who don’t want to hear it or believe it or make policy. The field is extremely lucky to have many people and groups working on its behalf, including but not limited to, the important work of SCN and EHN, CHE, TEDX, EDCfree and the NGO community, the Endocrine Society and many more around the globe. Nonetheless the EDC field has, no formal structure or organization, to help with planning, collaboration or coordination and outreach etc.

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1. Significant impacts of EDCs on human health: major accomplishments/ how were they accomplished/lessons learned

Commented [JPM1]: Do you include people who make corporate policy about what to include in their products? Chemists who make decisions about what design criteria they use in the synthesis of new chemicals? And especially consumers who make decisions about what to buy. Also lawyers deciding whom to sue over what. These audiences are going to be much more important for the next 3 years than regulators, at least in the US.

Commented [JPM2]: Do we want a “formal structure or organization?” Or a forum that increases communication and collaboration. Formal structures are easy to attack.

Commented [RZ3]: One issue here is how clinicians can begin to use EDC information? Along these lines, Loretta Doan (now the VP of American Association of Clinical Chemists) is trying to get the issue of EDCs discussed there. She might be a useful participant to this meeting?

Commented [JPM4]: I think this is the wrong word... too reminiscent of central planning by the USSR. Didn’t work for them. Instead think of it as “identifying strategic needs and opportunities to advance the field and encourage strategic collaborations.”

Commented [JPM5]: The big opportunities in the US in the near term are efforts to bolster consumer interest in safer products, coordination with lawyers around lawsuit opportunities and collaboration with chemists on chemical design. A longer range view might include building/strengthening ties between medical professional groups like Endo whose health goals are impaired by EDCs.

Commented [JPM6]: The only useful discussion here in the US for the next 3 years is “where is Trump going to attack/undermine EDC policy and what opportunities do we have to avert that.”

Commented [JPM7]: If we have participants from the EU then part of the program should focus on what’s next in that battle.

Commented [JPM8]: I hope that time spent on “lessons learned” is limited to specific information useful to evaluating future activities, e.g., “we tried that here xxx and it didn’t work, so let’s not go that way now” I would be especially interested in a session that asks “what are the big health challenges in endocrinology that have not yet been examined through an EDC lens, and how might that happen”
1. Because “EDCs” by definition interfere with hormones, I’m wondering if this plenary can focus on those research questions that are common among all EDCs. In my experience, some EDC work actually uncovers new ways of understand the basic endocrinology/biology whereas other kinds of studies highlights how regulators should change the way they think about things (i.e., “applied”). I’m wondering if this could be distilled across endocrine systems?

2. EDC research needs to improve impact of research/ new approaches/technologies
   
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Commented [JPM10]: I think a much more interesting and fun exercise would be to break into 4 groups, each composed of a mix of skills (science, communications, advocacy, legal), and ask them to brainstorm over a strategic campaign of their choosing.
3. How do we get the endocrine perspective of EDCs into toxicology, OECD, regulatory (EFSA, ECHA...) and industry
4. How can we talk to industry...are their industries and people we can “communicate” with? What can we learn from them?
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genius!

On Jul 24, 2017, at 8:53 PM, Vomsaal, Frederick S. <VomsaalF@missouri.edu> wrote:

I agree with Pete Jun is one of the few old guard EDC experts still really active in Japan and Steve is obviously as good as it gets having whipped Syngenta.
Now we need someone like Jun from the EU.
We had not thought about Andreas Gies.
Thats great, Bruce. Kudos for having brought them in!!!!

On Jul 24, 2017, at 8:37 PM, Bruce Blumberg <blumberg@uci.edu> wrote:

Hi everyone,

Jun Kanno and Steve Tillery are both definite attendees.

Best,

Bruce

On 7/23/2017 12:31 PM, Pete Myers wrote:

and especially great re Tillery!
the letter is great but I would advise reshuffling a little bit.

Currently:
Not only is it inappropriate for academic researchers to conduct GLP studies, it is also virtually impossible for a range of reasons. Academic researchers lack the necessary laboratory accreditation and funding for these large, traditional toxicology studies. Additionally, academic researchers cannot obtain the approval of Institutional Animal Care and Use Committees for studies using the large number of animals and endpoints required in GLP toxicity studies. Importantly, however, in contrast to GLP studies, the peer review system used in academia acts to ensure the robustness of academic data.

Alternative. Importantly, rather than focusing on record-keeping to avoid fraud, as does the GLP system, the peer review process used in academia focuses on scientific quality of research, about which GLP does nothing. Peer-review acts to ensure the robustness and quality of academic data. Moreover, NIH guidelines prohibit academic research from using the large number of rodents typically employed in GLP research, because statistical analysis shows those numbers are not necessary. Criticizing our research because it is not GLP is simply a red-herring that fails to understand how science achieves quality.

On Oct 5, 2014, at 9:31 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

<Response to Hostetler letter-10-5.docx>
From: Patricia Hunt <pathunt@vetmed.wsu.edu>
To: Pete Myers <jpmyers@ehsic.org>
Subject: Re: letter to McCarthy and Hamburg

Hi Pete-

I know that I am a pain, but I have to say that I still find this letter difficult to understand. The first paragraph is particularly difficult (I took a stab at it see attached) and I must say that I don't think the "scientific inaccuracies" come through clearly in the letter. I understand that other documents will be attached, but I'd really like McCarthy and Hamburg to be able to "get it" and understand exactly what you want them to address from the letter alone.

I will understand if you don't wish to incorporate my suggestions and still will sign.

Pat

From: Pete Myers <jpmyers@ehsic.org>
Date: Wednesday, June 4, 2014 8:07 AM
To: Fred Vom Saal <vomsaalF@missouri.edu>, Amy Kostant <amy@sciencecom.org>, Terry Collins <tc1u@andrew.cmu.edu>, "CranmerJoanM@uams.edu" <CranmerJoanM@uams.edu>, "deborah_cory-sleight@urmc.rochester.edu" <deborah_cory-sleight@urmc.rochester.edu>, Peter DeFur <pldefur@igc.org>, "sgilbert@innd.org" <sgilbert@innd.org>, "Prof. Louis J. Guillette" <lou.guillette@gmail.com>, "tyrone@berkeley.edu" <tyrone@berkeley.edu>, "Dr. Steve Heilig" <heilig@sfms.org>, "Hunt, Patricia Ann" <pathunt@wsu.edu>, Richard Jackson <dickjackson@ucla.edu>, "montee@earthlink.net" <montee@earthlink.net>, Philip Landrigan <phil.landrigan@mssm.edu>, "BLanphear@sfu.ca" <BLanphear@sfu.ca>, "hlnlead@pitt.edu" <hlnlead@pitt.edu>, Peter Orris <porris@uic.edu>, "dozonoff@bu.edu" <dozonoff@bu.edu>, "gprins@uic.edu" <gprins@uic.edu>, Ted Schettler <tschettler@igc.org>, Howard Snyder <snyderh@email.chop.edu>, Shanna Swan <shanna.swan@mssm.edu>, Bernard Weiss <bernard_weiss@urmc.rochester.edu>, "Woodrufft@obgyn.ucsf.edu" <Woodrufft@obgyn.ucsf.edu>, "R. Thomas Zoeller" <tzoeller@bio.umass.edu>, "shuk-mei.ho@uc.edu" <shuk-mei.ho@uc.edu>, "Stahlhut, Richard W." <stahlhutr@missouri.edu>, Bruce Blumberg <blumberg@uci.edu>, Sarah Vogel <svogel@edf.org>, Laura Vandenberg <lvandenbergschoolph.umass.edu>, "carl-gustaf.bornehag@kau.se" <carl-gustaf.bornehag@kau.se>, Russ Hauser <RHAUSER@hohp.harvard.edu>, Leonardo Trasande <leonardo.trasande@nyu.edu>, "kkreider@unfoundation.org" <kkreider@unfoundation.org>, "itescu@UCMAIL.UC.EDU" <itescu@UCMAIL.UC.EDU>, Michael Antoniou <michael.antoniou@kcl.ac.uk>, Emily Copeland <emily@sciencecom.org>, Gabriela Silvani <gabriela@sciencecom.org>

Subject: letter to McCarthy and Hamburg

Here's a new draft which I think has incorporated all the concerns raised by the last draft. So far, the list of signees includes the following, contingent upon editing

- Shanna
- Bernie
- Michael A.
- Terry
- Tom
- CG B
- Steve Gilbert
- Mei
- Howard
- Lou
- Bruce Lanphear
- Bruce Blumberg
- Fred
- David O
- Pat
- Dick Jackson, if edited
Dear Administrator McCarthy and Commissioner Hamburg,

We are writing with to express concern about the analysis of science presented in a key work report product written developed by scientists within your agencies. In the interest of protecting scientific integrity and public opinion, we request that you address the scientific inaccuracies highlighted below and documented in attached materials, be addressed by you to protect scientific integrity and public health.

At issue is a draft report analyzing non-monotonic dose responses (NMDRs) in studies of endocrine disrupting chemicals, written by EPA and FDA scientists and submitted to the National Academies of Science for review. The NAS review has now been published: Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disrupters (http://www.nap.edu/catalog.php?record_id=18608).

NMDRs have been shown to be a common feature of hormones and hormonally active chemicals. This challenges the central tenet of chemical risk assessments: that effects at high doses predict effects at low doses. It thus invalidates standard methods used to develop safety estimates for endocrine disrupting chemicals. Many estimates of ‘safe’ levels of exposure are likely to be off by orders of magnitude.

The NAS review identified a series of profound weaknesses in the processes used to develop the document, and recommended that the effort be restarted. The EPA has acknowledged such limitations and has indicated that it plans to conduct more systematic literature searches, data extraction, and evaluations of the evidence on NMDR curves.

As researchers with extensive knowledge in this field, we are concerned because, without systematically reviewing the literature, EPA and FDA scientists concluded that their current approach to NMDRs is effective without having systematically reviewed the literature. This suggests that these scientists have reached this conclusion without serious consideration of important available scientific evidence.

We recommend that a comprehensive review of the NAS document be undertaken and strongly encourage you to recruit the expertise of The Endocrine Society and other scientific societies who offered in a 2012 letter to Science Magazine to help with such reviews. These societies represent more than 40,000 medical and research professionals. All of the undersigned also offer their expertise to help in this review.

Because of its charge, the NAS panel limited itself solely to issues of process, and many of the issues identified in the NAS report mirror ones that were raised in oral and written comments submitted to the NAS during their review process. These comments, however, went further and identified scientific inaccuracies in how the EPA and FDA scientists presented the scientific literature in the EPA review.

We are attaching an overview of our concerns in the form of public testimony presented to the NAS review panel at its first meeting in Washington, DC and a much more detailed set of comments prepared by a subset of the undersigned. Both documents were submitted for the record in July 2013.
We ask that these concerns be formally reviewed by you and appropriate offices within your agencies. Too much is at stake for the health of Americans for us to rely on anything but the very best science.

If it would be helpful, we would be pleased to meet with you to discuss our concerns.

Thank you for your time and consideration.

Sincerely
I am sorry to hear about Theo that is far more important than this letter. Go to bed. I leave for Paris tomorrow and will tell Terry to go ahead and submit the letter (Fred thought it was great).

It's 3am and I'm jetlagged in Zurich. Spent last week with Theo in Paonia. She is dying. Very emotionally exhausting. lost all track of email. Will dig it out. Sorry.

On Oct 6, 2014, at 9:13 PM, Hunt, Pat <pathunt@vetmed.wsu.edu> wrote:

Hey Pete-

Do you have any comments on the letter?

Pat
I blew that. You are not half the many your father was!

> On Aug 7, 2015, at 11:16 AM, Pete Myers <jpmymers@ehsic.org> wrote:
> 
> You remember correctly! ☣ "You are not the man your father was!"
> 
> 
> >> On Aug 7, 2015, at 11:07 AM, Richard Stahlhut <richard.stahlhut@me.com> wrote:
> >>
> >> Sigh. Agreed.
> >>
> >> And if I remember right, he delivered the best one-liner ever uttered in Congress.
> >>
> >>
> >>> On Aug 7, 2015, at 9:55 AM, Ozonoff, David M <dozonnoff@bu.edu> wrote:
> >>>
> >>> Oh, my. Very sad news.
> >>>
He was so important in changing the conversation, a lasting legacy.

dave

On Aug 7, 2015, at 7:18 AM, Pete Myers <jpmyers@ehsic.org> wrote:

Passed away yesterday. I heard from his family a few minutes ago confirming this reality.

"He had a virus this last week, His son Matt had taken him in on Monday to the ER but they just gave him antibiotics and rest. He was ok on Tuesday, but Wednesday night felt even worse. We took him into the hospital, but there was nothing they could do as his immune system was depressed from the lymphoma.²

He gave us so much.

David Ozonoff, MD, MPH
Professor of Environmental Health
Boston University School of Public Health
715 Albany Street, Talbot West Room 430
Boston, MA 02118
USA
tel. 617 638-4620
fax 617 638-4857
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Hi Amy-

Sorry for the delayed response. I've been busy with my dad. We are having a great time and I am trying to get a bunch of little stuff that he can no longer do done while I am here. I fly home tomorrow and, if I don't get it done before I leave, I will write a brief summary for you on the plane tomorrow. I contacted the journal and asked them not to post the accepted version, so the paper will be embargoed until the final is ready for publication. We don't have a date yet, but our response to their changes went back yesterday, so I assume we have a week or two.

It was so lovely to see you. I could talk to you all day long!

I'll be back in touch soon,

Pat

From: Amy Kostant <amy@sciencecom.org>
Date: Friday, June 23, 2017 at 5:55 PM
To: patricia hunt <pathunt@vetmed.wsu.edu>
Subject: lovely day

Thank you for a wonderful lunch, but mostly for such a lovely afternoon!
I do wish you lived closer and we could do that more often. Actually, I wish we all lived in Paris where we could do this daily.

On Monday I'll send my pass at a note to journalists for your review, but if you send me the key points in plain language, I promise to send something better.
Confirming that I'll get in touch with the journal to request a pub date and embargo. Do you have a name and email address for the editor you're working with on this paper?

Have a safe and restful flight tomorrow, and enjoy seeing your father.

xoxox

Amy