To: Goldstein, Bernard D[bdgold@pitt.edu]
Cc: pinfante@starpower.net[pinfante@starpower.net]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Hudak, Juliann Marie[jmh206@pitt.edu]
From: Kurt Straif
Sent: Fri 5/27/2016 6:36:53 PM
Subject: RE: Is there a forthcoming IARC meeting on benzene??

We are in the midst of the hot phase of a Monographs meeting, will respond asap

Kurt

From: Goldstein, Bernard D [mailto:bdgold@pitt.edu]
Sent: 27 May 2016 17:59
To: Kurt Straif <StraifK@iarc.fr>; straif@iarc.fr
Cc: pinfante@starpower.net; Cogliano, Vincent <cogliano.vincent@epa.gov>; Hudak, Juliann Marie <jmh206@pitt.edu>
Subject: RE: Is there a forthcoming IARC meeting on benzene??

Hi Kurt

I've attached our planned poster. The key points we make supplement the valuable exchange that Peter and you and your colleagues made in print. Our basic argument is that irrespective of whether the epidemiological evidence raises to the level of sufficiency, benzene should be considered to be a known cause of NHL. Our major points are:

1. Benzene should be considered a known cause of NHL based on current IARC rules which state: IARC now considers a chemical to be a Group 1 carcinogen when there is less than sufficient evidence in humans but sufficient evidence in animals and "**strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity"** (my emphasis). While we can argue about whether the epi data is "sufficient" there can be no question about lymphoma in animals (I count seven studies and Peter counts ten). Further, with a superabundance of laboratory data on genotoxicity, and with lymphocyte chromosomal abnormalities routinely reported in the circulating lymphocytes of exposed workers there can be no question about the presence of a genotoxic mechanism relevant to humans

2. The outcome of the 2009 IARC deliberations on benzene and NHL is hauntingly similar to

the 1974 IARC review of benzene and AML in its overdependence on cohort-based epidemiology.

3. In 1974 there was a legitimate scientific argument about whether lymphocytic and myelocytic cells arose from the same stem cell. That argument has been settled in favor of a single precursor cell which is clearly affected by benzene in causing AML. Further, benzene has a promiscuous effect in causing multiple chromosomal abnormalities, again consistent with a causal role in NHL

4. Most disappointing is that the modification of the IARC process to include mechanistic information, on which you and Vincent (whom I have copied) and your colleagues worked so hard and so eloquently, has apparently failed in this case.

I do strongly suggest that benzene and NHL be subject to an IARC review. And I know that Peter feels strongly, as I do, in suggesting a review of workers exposed to gasoline. This is an important global issue, particularly in view of the large number of exposed workers and because it brings up some of the knotty mixture issues in relation to a known human carcinogen.

Looking forward to seeing you in Lyon

Bernie

From: Kurt Straif [mailto:StraifK@iarc.fr]
Sent: Monday, May 2, 2016 5:51 AM
To: Goldstein, Bernard D <bdgold@pitt.edu>; straif@iarc.fr
Cc: pinfante@starpower.net
Subject: RE: Is there a forthcoming IARC meeting on benzene??

Dear Bernie,

I look forward to welcoming you to the IARC conference – we all expect this will be a great meeting with lots of new science that impacts on public health and a great opportunity to welcome many friends to Lyon.

I am curious to read and discuss your poster. A new benzene Monograph has not yet been firmly scheduled.

Best wishes,

Kurt

From: Goldstein, Bernard D [mailto:bdgold@pitt.edu]
Sent: 30 April 2016 19:17
To: straif@iarc.fr
Cc: pinfante@starpower.net
Subject: Is there a forthcoming IARC meeting on benzene??

Hi Kurt

Hope all is well with you and your colleagues. As you probably know, Peter Infante and I have a poster presentation at the 50th Anniversary meeting on benzene and NHL in June. We argue that the delay in the recognition of benzene as a known cause of NHL mirrors the initial delay in the recognition of benzene as a known cause of ANLL, and fails to take into account the mechanistic evidence.

I recall there was talk of a future IARC meeting in which benzene would again be reviewed with a focus on NHL and other non-ANLL cancers. I could not find any mention of such a meeting on the IARC website. I am preparing the poster now, and if such a meeting is being scheduled by IARC I would welcome including such a statement within the poster material

Best personal regards – and I look forward to seeing you in June

Bernie

Bernard D. Goldstein, MD

Emeritus Professor and Emeritus Dean

Graduate School of Public Health

University of Pittsburgh

Rm A710 Crabtree Hall

130 De Soto St

Pittsburgh, PA 15261

Phone 412 648 9994

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To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Marie-Monique Robin
Sent: Wed 5/11/2016 4:17:57 PM
Subject: Re: from Marie-Monique

Thank you, Vincent.
If you come to Paris with your family, please tell me! I am a good (organic) cooker!
Just a question: could you recommend me a nice (not too expansive) hotel in Washington?
Warm regards,
Marie-Monique

2016-05-11 17:58 GMT+02:00 Cogliano, Vincent <cogliano.vincent@epa.gov>:

> Bonjour Marie-Monique—It's good to hear from you again and to read about your recent activities.
>
> Regarding glyphosate, my program is not involved, and I don't know who might be the appropriate person to interview. In addition, requests for interviews must go through the EPA's media office. I'm copying my media liaison on this message so that he can forward it to the EPA's central media office.
>
> I'm sorry that I'll miss your visit to the U.S. During the entire time of your visit I'll be on vacation to watch my daughter graduate from veterinary school.
>
> With warm regards and best wishes on your new project,
>
> Vincent
>
> **From:** Marie-Monique Robin [mailto:m2rbox@gmail.com]
> **Sent:** Monday, May 02, 2016 4:40 PM
> **To:** Cogliano, Vincent <cogliano.vincent@epa.gov>
> **Subject:** from Marie-Monique
>
> Dear Vincent,
>
> I hope you are doing well.
>
> After we met for my documentary and book Our Daily Poison which have both been released in the USA (thenewpress.com/books/our-daily-poison and http://icarusfilms.com/new2011/pois.html),

I decided to switch to "positive investigations" showing that there are alternatives to this crazy world (!) and made two documentaries and books called "Crops of the Future" and "Good Old Growth"
(http://www.harmonywithnatureun.org/index.php?page=view&type=12&nr=30&menu=195&str=&pub_year=0&language=

I said that I will never touch any controversial topic anymore...

That was not true!

I am preparing a new film (and book) about ... glyphosate and I recently interviewed your successor Dr. Kurt Straif, who is a very nice person. By the way he is also very upset with the Bfr's and EFSA's position who are rejecting the IARC's classification of glyphosate. This is quite interesting...

I plan to go to the USA between May 21st and 25th and I would like to interview a EFSA's representative about the reapproval process of glyphosate. What do you recommend me? Who would be the right person to interview?

Thank you for your help!

Warm regards,

Marie-Monique

www.m2rfilms.com

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Ross, Mary
Sent: Mon 5/9/2016 3:11:22 PM
Subject: RE: questions regarding IARC

Ex. 5 - Deliberative Process

From: Cogliano, Vincent
Sent: Monday, May 09, 2016 11:05 AM
To: Ross, Mary <Ross.Mary@epa.gov>
Subject: FW: questions regarding IARC

Ex. 5 - Deliberative Process

From: Zeise, Lauren@OEHHA [mailto:Lauren.Zeise@oehha.ca.gov]
Sent: Friday, May 06, 2016 12:32 PM
To: Cogliano, Vincent <cogliano.vincent@epa.gov>
Cc: Monahan-Cummings, Carol@OEHHA <Carol.Monahan-Cummings@oehha.ca.gov>
Subject: questions regarding IARC

Vince,

We are in litigation on a matter involving IARC. Would you be available to answer questions that our attorneys have related to the operation of the Monographs program? If so, Carol Monahan-Cummings our chief counsel or Susan Fiering of the Attorney General's office may be

following up with you. Is this the best number to reach you at: 703-347-0220

I hope you are doing well. Wonderful seeing so much activity in your EPA program.

Best,

Lauren

Lauren Zeise, PhD, Acting Director

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

1515 Clay Street, 16th floor, Oakland, CA 94612

Lauren.Zeise@oehha.ca.gov (916) 322-6325 (Mon, Weds); (510) 622-3190 (Tu, Th, Fr)

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Monahan-Cummings, Carol@OEHHA[Carol.Monahan-Cummings@oehha.ca.gov]
From: Zeise, Lauren@OEHHA
Sent: Fri 5/6/2016 4:31:46 PM
Subject: questions regarding IARC

Vince,

We are in litigation on a matter involving IARC. Would you be available to answer questions that our attorneys have related to the operation of the Monographs program? If so, Carol Monahan-Cummings our chief counsel or Susan Fiering of the Attorney General's office may be following up with you. Is this the best number to reach you at: 703-347-0220

I hope you are doing well. Wonderful seeing so much activity in your EPA program.

Best,

Lauren

Lauren Zeise, PhD, Acting Director

OEHHA
SCIENCE FOR A HEALTHY CALIFORNIA

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

1515 Clay Street, 16th floor, Oakland, CA 94612

Lauren.Zeise@oehha.ca.gov (916) 322-6325 (Mon, Weds); (510) 622-3190 (Tu, Th, Fr)

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Wed 5/4/2016 4:57:59 PM
Subject: Bonjour!

Bonjour, Vincent!

I hope you are well. Perhaps you may have seen this article: http://www.huffingtonpost.com/carey-gillam/what-is-going-on-with-gly_b_9825326.html ? We were wondering what the story was behind this "accidental" release, and whether it is within the remit of OPP is to comment on and critique an IARC evaluation. Are you aware of any precedent?

Tomorrow is a national holiday- and naturally we will make the "pont" to the weekend. :-)

Best wishes,
Kate

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Marie-Monique Robin
Sent: Mon 5/2/2016 8:40:09 PM
Subject: from Marie-Monique

Dear Vincent,

I hope you are doing well.
After we met for my documentary and book Our Daily Poison which have both been released in the USA (thenewpress.com/books/our-daily-poison and http://icarusfilms.com/new2011/pois.html),
I decided to switch to "positive investigations" showing that there are alternatives to this crazy world (!) and made two documentaries and books called "Crops of the Future" and "Good Old Growth"
(http://www.harmonywithnatureun.org/index.php?page=view&type=12&nr=30&menu=195&str=&pub_year=0&language=0&
I said that I will never touch any controversial topic anymore...
That was not true!
I am preparing a new film (and book) about ... glyphosate and I recently interviewed your successor Dr. Kurt Straif, who is a very nice person. By the way he is also very upset with the Bfr's and EFSA's position who are rejecting the IARC's classification of glyphosate. This is quite interesting...
I plan to go to the USA between May 21st and 25th and I would like to interview a EFSA's representative about the reapproval process of glyphosate. What do you recommend me? Who would be the right person to interview?
Thank you for your help!
Warm regards,
Marie-Monique
www.m2rfilms.com

To: IARC Monograph 118[monograph118@iarc.fr]
Cc: Hotchkiss, Andrew[Hotchkiss.Andrew@epa.gov]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Fritz, Jason
Sent: Tue 4/26/2016 1:49:31 PM
Subject: Re: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France
vol118-doi_JF.docx

Drs. Guha and Straif,

Thank you for your offer: I would be most excited to join the IARC working group in this effort! Attached please find my completed DOI form. I'll admit I wasn't sure what to do with the "insert picture" field underneath the signature line: did you need me to take a picture of my signature and attach that?

Please don't hesitate to contact me if there is any further information I can provide, and thanks again.

Jason Fritz

Jason M. Fritz, Ph.D.
Associate for Chemical Assessment (acting), Toxicity Pathways Branch
Toxicologist
U.S. EPA
ORD/NCEA/IRIS
1200 Pennsylvania Ave., N.W.
Washington, D.C., 20460
703-347-0332

From: IARC Monograph 118 <monograph118@iarc.fr>
Sent: Monday, April 25, 2016 11:21 AM
To: Fritz, Jason
Subject: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

Preliminary Invitation

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

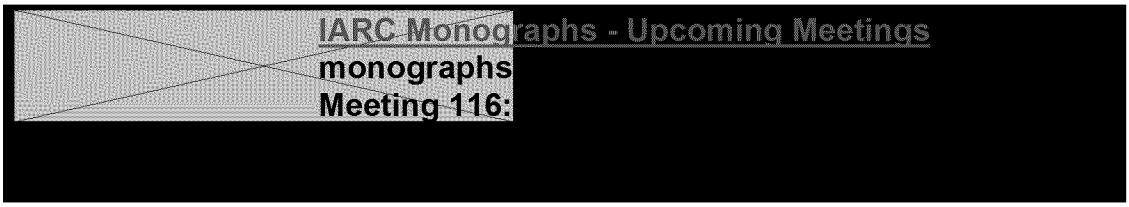
Volume 118 – 'Welding, Welding Fumes and Some Related Chemicals'

21-28 March 2017

Lyon, France

Dear Dr Fritz,

The International Agency for Research on Cancer (IARC) is convening a meeting to develop Volume 118 of the IARC Monographs on *'Welding, Welding Fumes and Some Related Chemicals'*. Information is available on the Monographs programme website at http://monographs.iarc.fr/ENG/Meetings/index.php.



In view of your knowledge and experience in the field, we are inquiring as to your interest and availability to serve on the Working Group of this Monograph. **Participation for the full duration of the meeting is expected** (Saturday included).

All participants will receive a writing assignment:

a. IARC will provide preliminary search results and articles in pdf; participants are also expected to search the scientific literature for additional studies; IARC will assist in retrieving articles if necessary.

b. The design and relevant results of each epidemiological study and cancer bioassay are summarised in text and tables; IARC will provide templates for the tables; mechanistic studies are summarized but are not described individually.

The working papers you write will be peer-reviewed by other participants and **you will be asked to peer-review working papers** produced by other participants.

Experience has shown that on-time completion of writing assignments is key to the efficiency of the meeting and the ultimate quality of the Monographs. The first drafts and revisions will be due several months in advance of the meeting. **We expect all participants to comply with the following schedule**:

01.11.2016	**Preliminary drafts and references due to IARC**
22.11.2016	**Peer-reviews due to IARC**

14.02.2017 **Revised drafts and references due to IARC**

IARC will provide a pre-paid ticket for travel to the meeting (by economy air or first-class train) and a cash per diem to cover hotel and living expenses in Lyon. (U.S. Government employees should note that no U.S. Government funds will be used for their expenses and no honorarium will be paid.)

Before IARC can consider sending an official invitation, all potential participants must complete the **World Health Organization's Declaration of Interests** (attached). If you are available and interested in participating, please complete and return the declaration as soon as possible by e-mail (monograph118@iarc.fr) or fax (+33-4-72.73.83.19).

Yours sincerely,

Neela Guha, PhD

Responsible Officer for the meeting

Kurt Straif, MD, PhD

Head, IARC Monographs Section

International Agency for Research on Cancer/Centre International de Recherche sur le Cancer

150, cours Albert Thomas

F-69372 Lyon Cedex 08

France

Tel: 33-4-72.73.83.67

Fax: 33-4-72.73.83.19

monograph118@iarc.fr

http://monographs.iarc.fr/

DECLARATION OF INTERESTS FOR IARC/WHO EXPERTS

IARC/WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise.** To ensure the highest integrity and public confidence in its activities, IARC/WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e. any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to IARC/WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a IARC/WHO activity can be confirmed.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a IARC/WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e. you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e. you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be **published** in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside IARC/WHO if the Director/Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name:	Jason M. Fritz
Institution:	United States Environmental Protection Agency
Email:	Fritz.Jason@epa.gov

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
Volume 118: Welding, Welding Fumes, and Some Related Chemicals
Lyon, France: 21–28 March 2017

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e. spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment — Yes ☐ No ☒

1b Consulting, including service as a technical or other advisor — Yes ☐ No ☒

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding — Yes ☐ No ☒

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) — Yes ☐ No ☒

2c Support (including honoraria) for being on a speakers bureau, providing speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work? — Yes ☐ No ☒

INVESTMENT INTERESTS

Do you have current investments (valued at more than US $1000) in a commercial entity with an interest related to the subject of the meeting or work?

Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g. short sales) — Yes ☐ No ☒

3b Commercial business interests (e.g. proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) — Yes ☐ No ☒

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications) — Yes ☐ No ☒

4b Proprietary know-how in a substance, technology or process — Yes ☐ No ☒

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? — Yes ☐ No ☒

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? — Yes ☐ No ☒

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? — Yes ☐ No ☒

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or

business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?

6c Excluding IARC/WHO, has any person or entity paid or contributed towards your travel costs in connection with this IARC/WHO meeting or work? Yes ☐ No ☒

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this IARC/WHO meeting or work? Yes ☐ No ☒

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☒

7 **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)*
Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes ☐ No ☒

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is **"yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

Nos. 1-4, 7: Type of interest, question number and category (e.g. Intellectual Property 4.a copyrights) and basic descriptive details	**Name of company, organization, or institution**	**Belongs to you, a family member, employer, research unit or other?**	**Amount of income or value of interest (if not disclosed, is assumed to be significant)**	**Current interest (or year ceased)**
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details. Click here to enter text.				

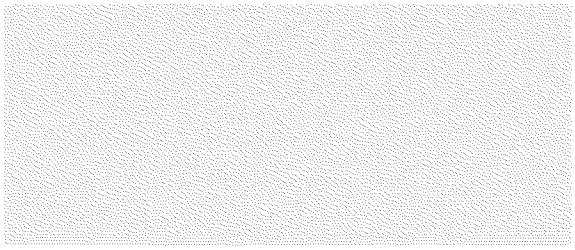
CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of IARC/WHO and complete a new declaration of interests form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

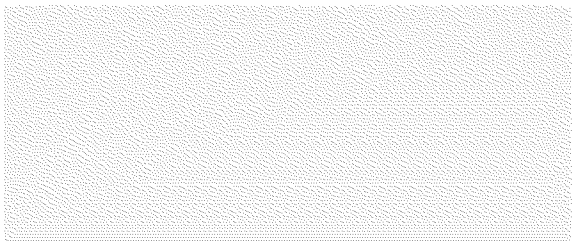
Date: 25 April, 2016

Signature: Jason Michael Fritz



Date: Click here to enter text.
(to be signed again at the meeting)

Signature: Click here to enter text.



To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Tue 4/26/2016 1:22:17 PM
Subject: Bonjour!

Bonjour, Vince!

I hope this finds you well. Spring? We've had some gorgeous days here, but not enough to put away my warm coat-- yet.

I have a question for you concerning ILSI. I have been corresponding with Catherine about her involvement in the v117 meeting. She mentioned that ILSI has been pressuring her to join a Technical Committee on Genetic Toxicology. You might find it of interest that ILSI's relationship with WHO has recently changed; since January 2015, ILSI no longer has non-state actor status with WHO (see http://www.who.int/about/collaborations/non-state-actors/en/) , due to ties with the tobacco industry (see http://www.who.int/tobacco/media/en/ILSI.pdf).
Accordingly, we have also been advised to take a cautious approach, considering that ISLI is also supported by other parties with interest in the v117 and other Monograph evaluations (see http://www.ilsi.org/Documents/Members.pdf).

All that said, I have advised Catherine that IARC would request that she disclose any formal involvement with ILSI that occurs before the meeting. While this opportunity could be seen as important for advancing her career, the perception is a bit more murky. At the same time, I was also wondering about any current policy or practice within NCEA/ORD/EPA concerning scientist's interactions with ILSI?

Thanks for your thoughts,
Best,
Kate

Kate Z. Guyton PhD DABT

Monographs Section

International Agency for Research on Cancer
150, cours Albert Thomas
69372 Lyon Cedex 08

France
Tel: [+33] (0)4 72 73 86 54

Guytonk@iarc.fr

To: Fritz, Jason[Fritz.Jason@epa.gov]
Cc: Hotchkiss, Andrew[Hotchkiss.Andrew@epa.gov]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Subramaniam, Ravi
Sent: Mon 4/25/2016 4:53:25 PM
Subject: Re: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

Hi Jason

Congratulations!!

Sent from my iPhone

On Apr 25, 2016, at 9:21 PM, Fritz, Jason <Fritz.Jason@epa.gov> wrote:

Hello,

I've been invited to serve on the IARC working group for Volume 118, meeting next year in March, 2017 as per the information below.

I would love to join this effort. May I accept this invitation?

Thank you,

Jason.

From: IARC Monograph 118 <monograph118@iarc.fr>
Sent: Monday, April 25, 2016 11:21 AM
To: Fritz, Jason
Subject: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

Preliminary Invitation

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

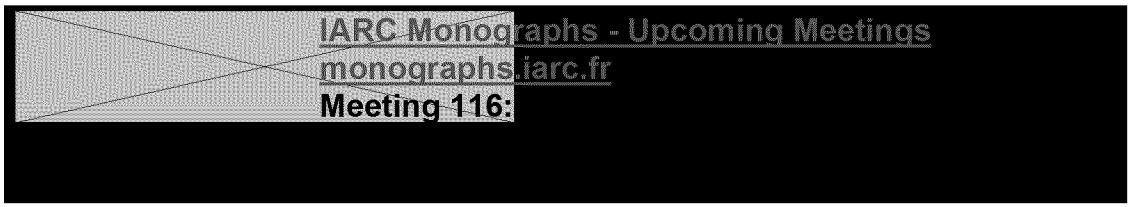
Volume 118 – 'Welding, Welding Fumes and Some Related Chemicals'

21-28 March 2017

Lyon, France

Dear Dr Fritz,

The International Agency for Research on Cancer (IARC) is convening a meeting to develop Volume 118 of the IARC Monographs on *'Welding, Welding Fumes and Some Related Chemicals'*. Information is available on the Monographs programme website at http://monographs.iarc.fr/ENG/Meetings/index.php.



In view of your knowledge and experience in the field, we are inquiring as to your interest and availability to serve on the Working Group of this Monograph. **Participation for the full duration of the meeting is expected** (Saturday included).

All participants will receive a writing assignment:

a. IARC will provide preliminary search results and articles in pdf; participants are also expected to search the scientific literature for additional studies; IARC will assist in retrieving articles if necessary.

b. The design and relevant results of each epidemiological study and cancer bioassay are summarised in text and tables; IARC will provide templates for the tables; mechanistic studies are summarized but are not described individually.

The working papers you write will be peer-reviewed by other participants and **you will be asked to peer-review working papers** produced by other participants.

Experience has shown that on-time completion of writing assignments is key to the efficiency of the meeting and the ultimate quality of the Monographs. The first drafts and revisions will be due several months in advance of the meeting. **We expect all participants to comply with the following schedule**:

01.11.2016 **Preliminary drafts and references due to IARC**

22.11.2016	**Peer-reviews due to IARC**
14.02.2017	**Revised drafts and references due to IARC**

IARC will provide a pre-paid ticket for travel to the meeting (by economy air or first-class train) and a cash per diem to cover hotel and living expenses in Lyon. (U.S. Government employees should note that no U.S. Government funds will be used for their expenses and no honorarium will be paid.)

Before IARC can consider sending an official invitation, all potential participants must complete the **World Health Organization's Declaration of Interests** (attached). If you are available and interested in participating, please complete and return the declaration as soon as possible by e-mail (monograph118@iarc.fr) or fax (+33-4-72.73.83.19).

Yours sincerely,

Neela Guha, PhD

Responsible Officer for the meeting

Kurt Straif, MD, PhD

Head, IARC Monographs Section

International Agency for Research on Cancer/Centre International de Recherche sur le Cancer

150, cours Albert Thomas

F-69372 Lyon Cedex 08

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http://monographs.iarc.fr/

<vol118-doi.docx>

To: Fritz, Jason[Fritz.Jason@epa.gov]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; Subramaniam, Ravi[Subramaniam.Ravi@epa.gov]
From: Hotchkiss, Andrew
Sent: Mon 4/25/2016 3:55:04 PM
Subject: RE: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

I would be supportive of you joining this effort. Vince, Ravi?

Best regards,

Andrew

From: Fritz, Jason
Sent: Monday, April 25, 2016 11:52 AM
To: Hotchkiss, Andrew <Hotchkiss.Andrew@epa.gov>
Cc: Cogliano, Vincent <cogliano.vincent@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>
Subject: Fw: Preliminary Invitation: IARC Monograpshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

Hello,

I've been invited to serve on the IARC working group for Volume 118, meeting next year in March, 2017 as per the information below.

I would love to join this effort. May I accept this invitation?

Thank you,

Jason.

From: IARC Monograph 118 <monograph118@iarc.fr>
Sent: Monday, April 25, 2016 11:21 AM

To: Fritz, Jason
Subject: Preliminary Invitation: IARC Monographshs, Vol 118 - 'Welding, Welding Fumes and Some Related Chemicals', 21-28 March 2017, Lyon, France

Preliminary Invitation

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

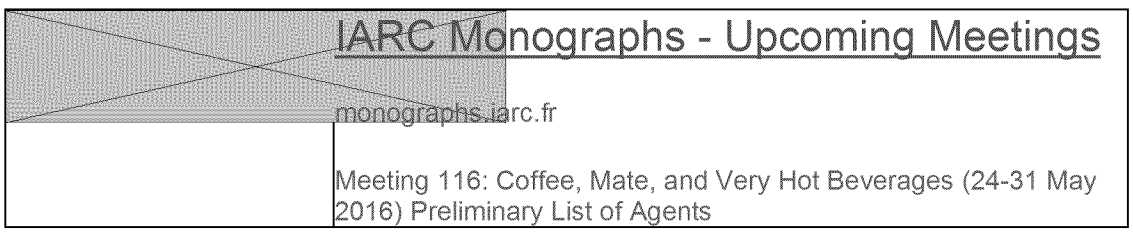
Volume 118 – 'Welding, Welding Fumes and Some Related Chemicals'

21-28 March 2017

Lyon, France

Dear Dr Fritz,

The International Agency for Research on Cancer (IARC) is convening a meeting to develop Volume 118 of the IARC Monographs on *'Welding, Welding Fumes and Some Related Chemicals'*. Information is available on the Monographs programme website at http://monographs.iarc.fr/ENG/Meetings/index.php.



In view of your knowledge and experience in the field, we are inquiring as to your interest and availability to serve on the Working Group of this Monograph. **Participation for the full duration of the meeting is expected** (Saturday included).

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Yours sincerely,

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monograph118@iarc.fr

http://monographs.iarc.fr/

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Nicolas Gaudin
Sent: Fri 4/1/2016 12:16:48 PM
Subject: Re: News Update: Johnson & Johnson Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Thanks Vincent,
Long time, no talk!
When are you traveling this way?
We miss you! For real! Your buddy Marie-Monique Robin was here last week…
It's *fin de règne* here…
Toutes mes amitiés,
Nicolas

From: <Cogliano>, Vincent <cogliano.vincent@epa.gov>
Date: Friday, April 1, 2016 2:04 AM
To: Kurt Straif <StraifK@iarc.fr>, Kathryn Guyton <GuytonK@iarc.fr>, Neela Guha <guhan@iarc.fr>, Dana Loomis <LoomisD@iarc.fr>, Baan Robert <robert.baan@69lyon03.org>, "grosse@iarc.fr" <grosse@iarc.fr>, Beatrice Lauby-Secretan <secretanb@iarc.fr>, El Ghissassi Fatiha <ElGhissassi@iarc.fr>, Bouvard Véronique <bouvard@iarc.fr>, Lamia Tallaa <tallaal@iarc.fr>, Hélène Lorenzen-Augros <lorenzen@iarc.fr>, Nicolas Gaudin <gaudin@iarc.fr>
Subject: Fwd: News Update: Johnson & Johnson Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Hello everyone—IARC is mentioned favorably in this article. How I miss working for a programme that gets good press! I hope you all are doing well ... With warm regards, Vincent

Begin forwarded message:

Subject: News Update: Johnson & Johnson

Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Johnson & Johnson Has a Baby Powder Problem

More than 1,000 women are suing the company for covering up a cancer risk.

By Susan Berfield, Jef Feeley, and Margaret Cronin Fisk | March 31, 2016

Photograph by Travis Rathbone

From

Jacqueline Fox worked in restaurant kitchens and school cafeterias, cleaned people's houses, watched their kids, raised a son, and took in two foster children. She was careful about her appearance and liked to tend the garden in front of her home in Birmingham, Alabama. She had been treated for high blood pressure, arthritis, and diabetes, but, at 59, she was feeling pretty good. In the spring of 2013, her poodle, Dexter, began acting strangely. He'd jump on her, he'd cry, he'd stay close by all day. Fox happened to watch a television program about a dog that sensed its owner was unwell. When she let Dexter sniff her, he whined even more.

A week later, Fox was diagnosed with advanced ovarian cancer. She had chemotherapy to shrink the tumors and surgery to remove her uterus, ovaries, fallopian tubes, and part of her spleen and colon. In December of that year, she saw a commercial from an Alabama law firm, Beasley Allen, suggesting a connection between long-term use of Johnson & Johnson's Baby Powder and

ovarian cancer. Fox had been sprinkling Baby Powder made from talc on her underwear every day since she was a teen. “I was raised up on it,” she later said in a deposition. “They was to help you stay fresh and clean. … We ladies have to take care of ourselves.” It was as normal as using toothpaste or deodorant. “We both were a bit skeptical at first,” says her son, Marvin Salter, a mortgage banker in Jacksonville, Fla. “It has to be safe. It’s put on babies. It’s been around forever. Why haven’t we heard about any ill effects?”

Fox and Salter in June 2014.

Source: Fox Family

Fox died from the cancer in October 2015. Four months later, a jury in St. Louis

concluded that talcum powder contributed to the development of the disease and thatJohnson & Johnson was liable for negligence, conspiracy, and failure to warn women of the potential risk of using Baby Powder in the genital area. The verdict, decided by a 10-2 vote, included $10 million in compensatory damages and $62 million in punitive damages, more than Fox's lawyers had recommended. Salter bowed his head and wept.

"People were using something they thought was perfectly safe," he says. "And it isn't. At least give people the choice. J&J didn't give people a choice." Among the most painful revelations, he says, was that in the 1990s, even as the company acknowledged concerns in the health community, it considered increasing its marketing efforts to black and Hispanic women, who were already buying the product in high numbers. Fox was black. The jury foreman, Krista Smith, says internal documents provided the most incriminating evidence: "It was really clear they were hiding something." She wanted to award the Fox family even more. Imerys Talc America, the biggest talc supplier in the country and the sole source of the powder for J&J, was also named as a defendant. The company wasn't found liable.

"Jury verdicts should not be confused with regulatory rulings or rigorous scientific findings," Carol Goodrich, a spokeswoman for Johnson & Johnson Consumer, said in an e-mail. "The overwhelming body of scientific research and clinical evidence supports the safety of cosmetic talc." The company says it will appeal the verdict. In a statement, Imerys said it's "confident that its products are safe for use by its customers. Our confidence is supported by the consensus view of qualified scientific experts and regulatory agencies."

Johnson & Johnson has spent more than $5 billion to resolve legal claims over its drugs and medical devices since 2013. That year, it agreed to pay $2.2 billion to settle criminal and civil probes into claims that it illegally marketed Risperdal, an antipsychotic drug, to children and the elderly; two other medicines were included in the settlement. It was one of the largest health fraud penalties in U.S. history. The company has also agreed to pay some $2.8 billion to resolve lawsuits about its artificial hips and $120 million for faulty vaginal-mesh inserts. In its 2015 annual report, J&J stated that more than 75,000 people had filed product liability claims, and that didn't include the talc powder cases.

More than 1,000 women and their families are suing J&J and Imerys, claiming the companies have known of the association with ovarian cancer for years and failed to warn them. The next trial is scheduled to begin on April 11 in a St. Louis

circuit court. “Whether or not the science indicates that Baby Powder is a cause of ovarian cancer, Johnson & Johnson has a very significant breach of trust,” says Julie Hennessy, a marketing professor at Northwestern’s Kellogg School of Management. “In trying to protect this one business, they’ve put the whole J&J brand at risk.”

“It has to be safe. It’s put on babies. It’s been around forever. Why haven’t we heard about any ill effects?”

Talc is the softest mineral on earth, able to absorb odors and moisture. It’s composed of magnesium, silicon, and oxygen and is mined, usually from deposits above ground, in more than a dozen countries. It’s used in eye shadow and blush and chewing gum, but mostly it’s used in ceramics, paint, paper, plastic, and rubber. China is the biggest source; Johnson & Johnson’s supply comes from the southern province of Guangxi.

Johnson & Johnson began selling Baby Powder more than 100 years ago, soon after the company was founded in New Brunswick, N.J. Among its first products were adhesives infused with pain relievers such as mustard seed, capsicum, quinine, and opium. When customers complained that removing the plasters left them with skin irritation, J&J’s scientific director sent them small containers of talc to help soothe any rashes. A few reported that the talc also seemed to ease diaper rash. In 1894 the company introduced Baby Powder, made of 99.8 percent talc and sold in a metal tin labeled “for toilet and nursery.”

The other 0.2 percent is a mix of fragrant oils. Smell is evocative, and this particular scent is mingled with powerful memories—a marketer’s dream. “It’s calming, nurturing. … It doesn’t grab your senses. It wafts,” Fred Tewell, a J&J executive, told the Associated Press in 2008. The company has said that in blind tests, the scent of Baby Powder is recognized more often than that of chocolate, coconut, or mothballs. From the early 1900s, J&J tried to persuade women to use the powder on themselves, too. Ads in 1913 included the tag line, “Best for Baby, Best for You.” By 1965, when Fox was 12 years old, ads featured a sultry woman sprinkling talc on her bare shoulder. No baby is in sight. “Want to feel cool, smooth and dry? It’s as easy as taking powder from a baby.” Two decades later, the company told the *New York Times Magazine* that 70 percent of its Baby

Powder was used by adults. Sales of J&J's talcum powder products came to about $374 million in 2014, according to Euromonitor. That's not essential to a $70 billion company that makes most of its money selling medical devices and drugs. But without Baby Powder, J&J may not have developed Baby Oil or Baby Shampoo nor have a baby division worth some $2 billion. Baby Powder's value to the company extends well beyond sales.

Forty-five years ago, British researchers analyzed 13 ovarian tumors and found talc particles "deeply embedded" in 10. The study, published in 1971, was the first to raise the possibility that talcum powder could pose a risk. In 1982 a study in the journal*Cancer* by Daniel Cramer, an epidemiologist at Brigham & Women's Hospital in Boston, showed the first statistical link between genital talc use and ovarian cancer. Soon after, Cramer received a call from Bruce Semple, an executive at J&J. The two met in Boston. "Dr. Semple spent his time trying to convince me that talc use was a harmless habit, while I spent my time trying to persuade him to consider the possibility that my study could be correct and that women should be advised of this potential risk of talc," Cramer, a paid expert and witness for the plaintiffs, said in a 2011 court filing. "I don't think this was a question of money," he says now. "I think it was pride of ownership. Baby Powder is a signature product for J&J."

Baby Powder is considered a cosmetic, which doesn't need to be approved by the Food and Drug Administration under the 1938 Food, Drug, and Cosmetic Act. The law is laid out in a 345-page document; only two pages are devoted to the safety of cosmetics. Congress is considering updating the law to give the FDA more authority to regulate products. "It shouldn't be up to consumer groups or jurors to try to make decisions about toxic products," says Stacy Malkan, co-founder of the Campaign for Safe Cosmetics. J&J and many other big companies support the changes.

J&J does have a warning on Baby Powder, cautioning against inhalation. And the label notes that the powder is for external use only. Under pressure from consumers, activists, and impending California safety regulations, J&J has removed triclosan, formaldehyde, and other so-called chemicals of concern from its baby products in the past few years. In 2013, Samantha Lucas, a company spokeswoman, explained the shift to *Scientific American*: "We've been replying with evidence of the science that ensures safety. Now we have to go beyond science and be responsive to our consumers, because it's really about their peace of mind." If J&J applies this same thinking to Baby Powder, it has an alternative: It already sells Baby Powder made from cornstarch for about the same price. No study shows that cornstarch poses any potential risks; the

American Cancer Society has been suggesting since 1999 that women consider it if they want to use genital powder. Some of J&J's competitors, including Gold Bond, California Baby, and Burt's Bees, sell baby powder made of cornstarch only.

Since Cramer's article was published, an additional 20 epidemiological studies have found that long-term perineal talc use increases the risk of ovarian cancer by about 33 percent. Yet other research has found no association. These mixed results have been cited by many agencies and institutions—with the exception of the International Agency for Research on Cancer (IARC) at the World Health Organization—when they've looked at a potential link. Roberta Ness, former dean of the University of Texas School of Public Health and former president of the American Epidemiological Society, testified at the Fox trial as an expert witness for the family. She argued that several of the studies showing no link didn't properly measure women's exposure to talcum powder. Some asked women how many years they had used the powder; others asked how often they used it. Only five measured both. "What's confused everyone in the past," she said during the trial, is that "all these studies, they looked at just frequency or just duration, and they're all over the map." She went on to explain that "all of the studies that have actually measured frequency and duration … have all shown a statistically significant trend toward more exposure causing more disease." Ness pointed out that the association between hormone therapy and breast cancer is statistically smaller than the reported association between talc and ovarian cancer, yet hormone therapy is considered to be a real risk.

She also said that not being able to prove how talc powder could contribute to cancer doesn't relieve a company of the responsibility to warn women of the association. "We now have data that suggest there's an association between the Zika virus and microcephaly," she said. And even though scientists don't know how the virus causes the disease, "people aren't waiting. … People are out there saying, 'Oh my gosh, be aware, this is trouble.'"

J&J and Imerys, the talc supplier, argue that the statistical associations between use of the powder and ovarian cancer are limited, weak, and based on unreliable data. They say a causal link isn't biologically plausible, because there's no proof that talc particles can move up through the reproductive tract or that once there they could cause cancer. And if there's no causal connection, they say there's no reason to add a warning to Baby Powder. "There are statistical correlations. You

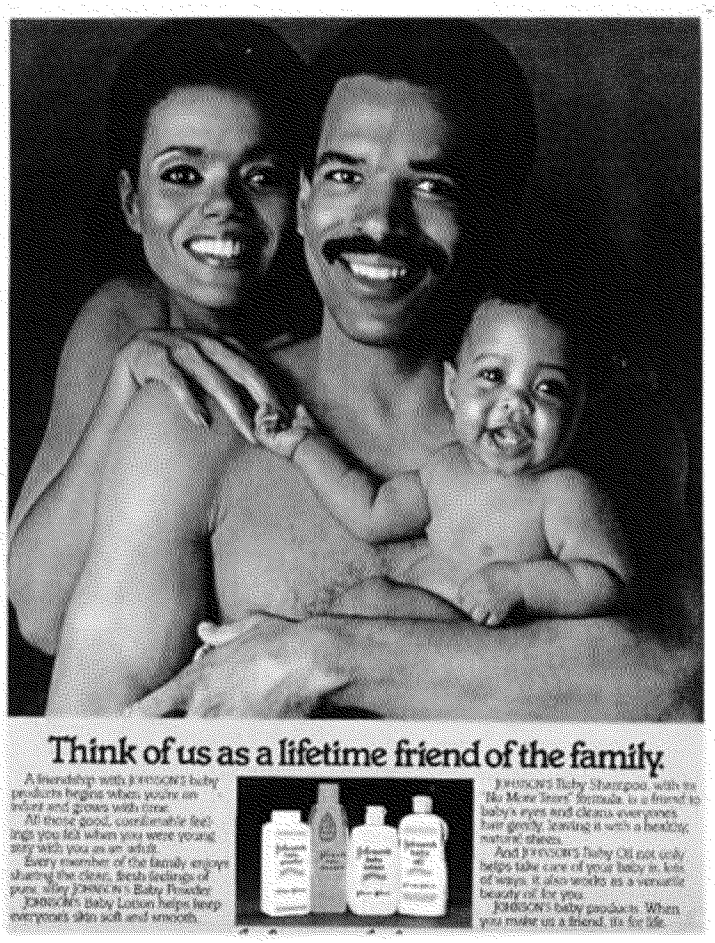
can always calculate correlations," says Joshua Muscat, a professor of public health sciences at Penn State College of Medicine who serves as an expert consultant to J&J. "There hasn't been a single scientific body that has considered talc to be a causal agent. Many don't even consider talc to be a risk factor. To me, the science is black and white."

The odds of a woman in the U.S. falling ill with ovarian cancer are 1 in 70. Talc use is associated with worse odds, 1 in 53, according to those epidemiological studies. The risks seem to be higher for invasive serous cancer, which Fox had. Ovarian cancer is among the most deadly cancers. Some 20,000 women are diagnosed each year, often after the disease has spread. The symptoms are easily dismissed as menstrual or abdominal discomfort. There's no regular screening for ovarian cancer, no known causes, only risk factors, and some research suggests the malignancy may begin outside the ovaries, at the end of the fallopian tubes. More than 14,000 women die from the disease every year.

At the Fox trial, Ness did some harsh math for the jury. She claimed that Baby Powder use could contribute to some 2,500 women being diagnosed with ovarian cancer every year and 1,500 dying. The defense counsel, with great skepticism, called that figure "astonishing." Ness also noted that although black women generally have lower odds than white women of getting ovarian cancer, a small study recently showed they're more at risk of developing ovarian cancer when exposed to talc.

In the last months of her life, Fox answered questions from attorneys on both sides of the case. The audio of her deposition was played in the courtroom near the end of the three-week trial. When asked why she was suing J&J, she said, "To put out there that we as women got to take care of ourselves. This is a disease I didn't ask for. But who am I? I just want to do right."

The science may be limited, and it may be ambiguous. Many of the researchers involved, including Cramer, say more study is necessary. But the science wasn't on trial in St. Louis; Johnson & Johnson was. "You don't win with jurors on science. They don't understand science, statistics, the design of studies," says Erik Gordon, a professor at the School of Business and School of Law at the University of Michigan. "They do understand there was some evidence of a connection between talc and cancer, and J&J didn't tell customers about it."



J&J ads from 1965 and 1980.

Ebony magazone ad: Gaslight Ad Archives

Lawyers for Fox introduced documents from 1986 through 2004 that, however selective they may be, portray a company struggling to revive interest in a symbolically important product with no proven health benefits and some suspected health risks. A 1992 memo outlining "major opportunities and major obstacles" acknowledged that "negative publicity from the health community on talc (inhalation, dust, negative doctor endorsement, cancer linkage) continues." The same memo included a recommendation to "investigate ethnic (African-American, Hispanic) opportunities to grow the franchise," noting that these women accounted for a high proportion of sales. An added handwritten note says the company planned a print advertising campaign. Goodrich, the J&J spokeswoman, said in her e-mail that this was "simply part of the company's efforts to appropriately understand who is using its products." More than a

decade later, a task force devoted to improving sales of Shower to Shower, a mix of talc and cornstarch marketed to women, concluded: “African American consumers in particular will be a good target with more of an emotional feeling and talk about reunions among friends, etc., team up with *Ebony* Magazine.” It suggested promotions in churches, beauty salons, and barbershops, and Patti LaBelle or Aretha Franklin as celebrity endorsers. Neither became a spokeswoman for the brand. It’s not clear how much of the rest of the plan was put into action, since the company had already been advertising to blacks.

It’s standard practice for companies to focus on their most committed customers. Airlines take care of business fliers; loyal shoppers get special deals at stores. “That’s probably what they were doing,” says Hennessy, the Kellogg marketing professor. “In today’s climate, though, that looks horrible. From the outside it looks like J&J is less concerned, not more concerned, about its most loyal users because of their ethnic origin.”

Baby Powder is a legacy brand in the black community. “Some people might say, ‘What’s wrong with companies recognizing women of color as important consumers?’ ” says Robin Means Coleman, a professor of communications studies and Afro-American Studies at the University of Michigan. “We do want that. But we do not want companies to market potentially carcinogenic products.”

Salter, Fox’s son, hadn’t been aware of the marketing documents until the trial. “When I heard about it, I was infuriated,” he says. “And so was the jury.”

In the 1990s a toxicologist named Alfred Wehner worked as an outside consultant for J&J. His official role was to help evaluate the research on ovarian cancer and talc and advise the company on its response. Unofficially, he was its scold. Wehner was on J&J’s side, but he was concerned that a cosmetics trade group (partly funded by the company) was mischaracterizing the scientific case for talc. “A true friend is not he who beguiles you with flattery but he who discloses to you your mistakes before your enemies discover them,” Wehner began a 1997 letter to Michael Chudkowski, J&J’s manager of preclinical toxicology. Wehner described statements on talc research from the group as inept, misleading, and outright false. Referring to a statement a few years earlier, he wrote: “At that time there had been about 9 studies (more by now) published in the open literature that did show a statistically significant association between hygienic talc use and ovarian cancer. Anybody who denies this risks that the talc industry will be perceived by the public like it perceives the cigarette industry: denying the obvious in the face of all evidence to the contrary.” He wanted the trade group to argue that the studies’ biological significance was questionable.

Cosmetic talc isn't a big part of Imerys's business. The company, formerly called Luzenac, primarily sells the mineral for industrial purposes. But until 2006, it also fought any suggestion that talc could be a potential carcinogen. In the late 1990s, according to a Luzenac memo introduced at the trial, executives visited the head of epidemiology at the University of California at Irvine for advice on how "to stop the rumor about Ovarian cancer." One suggestion: Get "two or three experts from the club" to make the scientific case. "The club" could refer to independent scientists Luzenac had worked with before, but Fox's lawyers argued for a more sinister interpretation—that these were scientists who would respond to industry pressure. They also suggested that Luzenac and J&J exerted influence over a government group. In 2000 scientists with the National Toxicology Program, part of the U.S. Department of Health and Human Services, voted 13-2 to list talc, used perineally, as a possible human carcinogen, according to Fox's lawyers, but the companies persuaded the NTP to defer an official decision on the status of talc. A Luzenac executive, Richard Zazenski, wrote to a colleague afterward: "We, the talc industry, dodged a bullet in December, based entirely over the confusion of the definition issue." He was referring to ambiguity over the composition of the talc studied because, until the early 1970s, some powder contained naturally occurring asbestos fibers. He also discussed a coming NTP review, saying, "Time to come up with more confusion!" Imerys declined to comment on the specifics of the trial, but one witness for the defense offered the possibility that Zazenski was joking. Goodrich, the J&J spokeswoman, said any suggestion by Fox's lawyers of improper influence is "merely an unsubstantiated allegation."

In 2006, the IARC, the WHO cancer agency, declared that perineal use of cosmetic-grade talc was possibly carcinogenic. It cited "a modest, but unusually consistent, excess in risk" and also noted that bias in the studies couldn't be ruled out. Publicly, Luzenac and J&J tried to diminish the significance of the designation; red meat and coffee are also included in this group of possible carcinogens.

Before the year ended, however, Luzenac stopped backing studies to prove talc's safety because the "horse has already left the barn," wrote one executive, noting that cosmetic companies had also cut funding. One of their primary arguments for doing so, he said, was that there were already too many studies showing an association with ovarian cancer "to stem the tide of negative sentiment." More important, Luzenac added a warning on the safety data sheet included with the 2,000-pound bags of talc it delivers to J&J: Perineal use of the powder is a possible risk factor for ovarian cancer.

“We, the talc industry, dodged a bullet in December. ... Time to come up with more confusion!”

Johnson & Johnson says it will continue to defend the safety of talc, and it does so on its website. There, in a section explaining its policies about ingredients, the company addresses concerns over formaldehyde, parabens, phthalates, and triclosan—chemicals with damaged reputations, and worse. In every case, J&J states that the chemicals haven’t been proven harmful or that they were used in small enough amounts to be safe, but the company decided to remove them from its productsanyway. “We understand that from your perspective, government regulations may not be your only consideration when it comes to the personal-care products you and your family use,” it says about parabens. For phthalates, the company says it recognizes that “the best way to keep your confidence was not to use it at all.”

Why not apply that same standard to talc? Goodrich said the company listens when consumers raise concerns about ingredients. But “few ingredients have the same demonstrated performance, mildness and safety profile as cosmetic talc.”

The first woman to sue Johnson & Johnson for not warning of the risks of talcum powder was Deane Berg, who was diagnosed with ovarian cancer in 2007. She says she turned down a $1.3 million out-of-court settlement because she didn’t want to sign a confidentiality clause. Her case went to trial in 2013 in a South Dakota federal court as she was in remission. The jury found J&J was negligent, but didn’t award Berg any damages.

After the Fox verdict, 17,000 people contacted her attorneys at Beasley Allen; the firm is looking into 2,000 of those, in addition to 5,000 potential claims it was already investigating. Its next case will be tried in the same St. Louis circuit court as Fox’s, which has a reputation for being sympathetic to plaintiffs. Gloria Ristesund’s trial is set for April. She used Baby Powder for 40 years and was diagnosed with ovarian cancer in 2011.

Among those waiting their turn is Tenesha Farrar, who was diagnosed with

Stage 3 ovarian cancer in 2013 and is represented by the Lanier Law Firm. Farrar, who's 40 and black, says she'd used Baby Powder and Shower to Shower (which J&J sold to Valeant in 2012) for the last two decades. "My grandmother and mother used it, and I learned from them," she says. After hearing about the J&J marketing document, she began crying. "I can't believe they singled us out." Farrar had chemotherapy and a full hysterectomy. She had to take off five months from her work as a clerk in a dialysis clinic outside St. Louis. She lost her health insurance because she exceeded the policy limits and had to skip her last chemo treatment. She and her husband eventually filed for bankruptcy. She's back at work now. "I have five children who depend on me," she says. "I will never use another J&J product again."

(Corrects the year that the Ebony *magazine J&J ad ran.)*

Student Services Contractor

Science Communications Team

National Center for Environmental Assessment

Office of Research and Development, U.S. EPA

O: (703) 347-0167

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kurt Straif
Sent: Fri 4/1/2016 7:11:25 AM
Subject: RE: News Update: Johnson & Johnson Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Thank you Vincent;

Don't be too jealous, Monsanto and the meat industry try with all their powers to get it their way, and our time spent on only glyphosate is enormous…

Yet, even this journalist (or deliberately, the industry) got simple things wrong ("red meat and coffee are also included in this group of possible carcinogens") – as you know, red meat is 2A

Just yesterday, we discussed again the possibility to update the talc Monograph, and I forwarded Cramer's latest in press paper to Dana.

Warmest regards,

Kurt

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: 01 April 2016 02:05
To: Kurt Straif <StraifK@iarc.fr>; Kathryn Guyton <GuytonK@iarc.fr>; Neela Guha <guhan@iarc.fr>; Dana Loomis <LoomisD@iarc.fr>; Baan Robert <robert.baan@69lyon03.org>; Grosse Yann <grosse@iarc.fr>; Beatrice Lauby-Secretan <secretanb@iarc.fr>; El Ghissassi Fatiha <ElGhissassi@iarc.fr>; Bouvard Véronique <bouvard@iarc.fr>; Lamia Tallaa <tallaal@iarc.fr>; Lorenzen-Augros Helene <lorenzen@iarc.fr>; Gaudin Nicolas <gaudin@iarc.fr>
Subject: Fwd: News Update: Johnson & Johnson Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Hello everyone—IARC is mentioned favorably in this article. How I miss working for a programme that gets good press! I hope you all are doing well ... With warm regards, Vincent

Begin forwarded message:

Subject: News Update: Johnson & Johnson Has a Baby Powder Problem - More than 1,000 women are suing the company for covering up a cancer risk (Bloomberg)

Johnson & Johnson Has a Baby Powder Problem

More than 1,000 women are suing the company for covering up a cancer risk.

By Susan Berfield, Jef Feeley, and Margaret Cronin Fisk | March 31, 2016

Photograph by Travis Rathbone

From

Jacqueline Fox worked in restaurant kitchens and school cafeterias, cleaned people's houses, watched their kids, raised a son, and took in two foster children. She was careful about her appearance and liked to tend the garden in front of her home in Birmingham, Alabama. She had been treated for high blood pressure, arthritis, and diabetes, but, at 59, she was feeling pretty good. In the spring of 2013, her poodle, Dexter, began acting strangely. He'd jump on her, he'd cry, he'd stay close by all day. Fox happened to watch a television program about a dog that sensed its owner was unwell. When she let Dexter sniff her, he whined even more.

A week later, Fox was diagnosed with advanced ovarian cancer. She had chemotherapy to shrink the tumors and surgery to remove her uterus, ovaries, fallopian tubes, and part of her spleen and colon. In December of that year, she saw a commercial from an Alabama law firm, Beasley Allen, suggesting a connection between long-term use of Johnson & Johnson's Baby Powder and ovarian cancer. Fox had been sprinkling Baby Powder made from talc on her underwear every day since she was a teen. "I was raised up on it," she later said in a deposition. "They was to help you stay fresh and clean. … We ladies have to take care of ourselves." It was as normal as using toothpaste or deodorant. "We both were a bit skeptical at first," says her son, Marvin Salter, a mortgage banker in Jacksonville, Fla. "It has to be safe. It's put on babies. It's been around forever. Why haven't we heard about any ill effects?"

Fox and Salter in June 2014.

Source: Fox Family

Fox died from the cancer in October 2015. Four months later, a jury in St. Louis concluded that talcum powder contributed to the development of the disease and thatJohnson & Johnson was liable for negligence, conspiracy, and failure to warn women of the potential risk of using Baby Powder in the genital area. The verdict, decided by a 10-2 vote, included $10 million in compensatory damages and $62 million in punitive damages, more than Fox's lawyers had recommended. Salter bowed his head and wept.

"People were using something they thought was perfectly safe," he says. "And it isn't. At least give people the choice. J&J didn't give people a choice." Among the most painful revelations, he says, was that in the 1990s, even as the company acknowledged concerns in the health community, it considered increasing its

marketing efforts to black and Hispanic women, who were already buying the product in high numbers. Fox was black. The jury foreman, Krista Smith, says internal documents provided the most incriminating evidence: “It was really clear they were hiding something.” She wanted to award the Fox family even more. Imerys Talc America, the biggest talc supplier in the country and the sole source of the powder for J&J, was also named as a defendant. The company wasn’t found liable.

“Jury verdicts should not be confused with regulatory rulings or rigorous scientific findings,” Carol Goodrich, a spokeswoman for Johnson & Johnson Consumer, said in an e-mail. “The overwhelming body of scientific research and clinical evidence supports the safety of cosmetic talc.” The company says it will appeal the verdict. In a statement, Imerys said it’s “confident that its products are safe for use by its customers. Our confidence is supported by the consensus view of qualified scientific experts and regulatory agencies.”

Johnson & Johnson has spent more than $5 billion to resolve legal claims over its drugs and medical devices since 2013. That year, it agreed to pay $2.2 billion to settle criminal and civil probes into claims that it illegally marketed Risperdal, an antipsychotic drug, to children and the elderly; two other medicines were included in the settlement. It was one of the largest health fraud penalties in U.S. history. The company has also agreed to pay some $2.8 billion to resolve lawsuits about its artificial hips and $120 million for faulty vaginal-mesh inserts. In its 2015 annual report, J&J stated that more than 75,000 people had filed product liability claims, and that didn’t include the talc powder cases.

More than 1,000 women and their families are suing J&J and Imerys, claiming the companies have known of the association with ovarian cancer for years and failed to warn them. The next trial is scheduled to begin on April 11 in a St. Louis circuit court. “Whether or not the science indicates that Baby Powder is a cause of ovarian cancer, Johnson & Johnson has a very significant breach of trust,” says Julie Hennessy, a marketing professor at Northwestern’s Kellogg School of Management. “In trying to protect this one business, they’ve put the whole J&J brand at risk.”

“It has to be safe. It’s put on babies. It’s been around forever. Why haven’t we heard about any ill effects?”

Talc is the softest mineral on earth, able to absorb odors and moisture. It’s

composed of magnesium, silicon, and oxygen and is mined, usually from deposits above ground, in more than a dozen countries. It's used in eye shadow and blush and chewing gum, but mostly it's used in ceramics, paint, paper, plastic, and rubber. China is the biggest source; Johnson & Johnson's supply comes from the southern province of Guangxi.

Johnson & Johnson began selling Baby Powder more than 100 years ago, soon after the company was founded in New Brunswick, N.J. Among its first products were adhesives infused with pain relievers such as mustard seed, capsicum, quinine, and opium. When customers complained that removing the plasters left them with skin irritation, J&J's scientific director sent them small containers of talc to help soothe any rashes. A few reported that the talc also seemed to ease diaper rash. In 1894 the company introduced Baby Powder, made of 99.8 percent talc and sold in a metal tin labeled "for toilet and nursery."

The other 0.2 percent is a mix of fragrant oils. Smell is evocative, and this particular scent is mingled with powerful memories—a marketer's dream. "It's calming, nurturing. … It doesn't grab your senses. It wafts," Fred Tewell, a J&J executive, told the Associated Press in 2008. The company has said that in blind tests, the scent of Baby Powder is recognized more often than that of chocolate, coconut, or mothballs. From the early 1900s, J&J tried to persuade women to use the powder on themselves, too. Ads in 1913 included the tag line, "Best for Baby, Best for You." By 1965, when Fox was 12 years old, ads featured a sultry woman sprinkling talc on her bare shoulder. No baby is in sight. "Want to feel cool, smooth and dry? It's as easy as taking powder from a baby." Two decades later, the company told the *New York Times Magazine* that 70 percent of its Baby Powder was used by adults. Sales of J&J's talcum powder products came to about $374 million in 2014, according to Euromonitor. That's not essential to a $70 billion company that makes most of its money selling medical devices and drugs. But without Baby Powder, J&J may not have developed Baby Oil or Baby Shampoo nor have a baby division worth some $2 billion. Baby Powder's value to the company extends well beyond sales.

Forty-five years ago, British researchers analyzed 13 ovarian tumors and found talc particles "deeply embedded" in 10. The study, published in 1971, was the first to raise the possibility that talcum powder could pose a risk. In 1982 a study in the journal*Cancer* by Daniel Cramer, an epidemiologist at Brigham & Women's Hospital in Boston, showed the first statistical link between genital talc use and ovarian cancer. Soon after, Cramer received a call from Bruce Semple, an executive at J&J. The two met in Boston. "Dr. Semple spent his time trying to convince me that talc use was a harmless habit, while I spent my time trying to persuade him to consider the possibility that my study could be correct and that women should be advised of this potential risk of talc," Cramer, a paid expert and

witness for the plaintiffs, said in a 2011 court filing. “I don’t think this was a question of money,” he says now. “I think it was pride of ownership. Baby Powder is a signature product for J&J.”

Baby Powder is considered a cosmetic, which doesn’t need to be approved by the Food and Drug Administration under the 1938 Food, Drug, and Cosmetic Act. The law is laid out in a 345-page document; only two pages are devoted to the safety of cosmetics. Congress is considering updating the law to give the FDA more authority to regulate products. “It shouldn’t be up to consumer groups or jurors to try to make decisions about toxic products,” says Stacy Malkan, co-founder of the Campaign for Safe Cosmetics. J&J and many other big companies support the changes.

J&J does have a warning on Baby Powder, cautioning against inhalation. And the label notes that the powder is for external use only. Under pressure from consumers, activists, and impending California safety regulations, J&J has removed triclosan, formaldehyde, and other so-called chemicals of concern from its baby products in the past few years. In 2013, Samantha Lucas, a company spokeswoman, explained the shift to *Scientific American*: “We’ve been replying with evidence of the science that ensures safety. Now we have to go beyond science and be responsive to our consumers, because it’s really about their peace of mind.” If J&J applies this same thinking to Baby Powder, it has an alternative: It already sells Baby Powder made from cornstarch for about the same price. No study shows that cornstarch poses any potential risks; the American Cancer Society has been suggesting since 1999 that women consider it if they want to use genital powder. Some of J&J’s competitors, including Gold Bond, California Baby, and Burt’s Bees, sell baby powder made of cornstarch only.

Since Cramer’s article was published, an additional 20 epidemiological studies have found that long-term perineal talc use increases the risk of ovarian cancer by about 33 percent. Yet other research has found no association. These mixed results have been cited by many agencies and institutions—with the exception of the International Agency for Research on Cancer (IARC) at the World Health Organization—when they’ve looked at a potential link. Roberta Ness, former dean of the University of Texas School of Public Health and former president of the American Epidemiological Society, testified at the Fox trial as an expert witness for the family. She argued that several of the studies showing no link didn’t properly measure women’s exposure to talcum powder. Some asked women how many years they had used the powder; others asked how often they used it. Only five measured both. “What’s confused everyone in the past,” she

said during the trial, is that "all these studies, they looked at just frequency or just duration, and they're all over the map." She went on to explain that "all of the studies that have actually measured frequency and duration … have all shown a statistically significant trend toward more exposure causing more disease." Ness pointed out that the association between hormone therapy and breast cancer is statistically smaller than the reported association between talc and ovarian cancer, yet hormone therapy is considered to be a real risk.

She also said that not being able to prove how talc powder could contribute to cancer doesn't relieve a company of the responsibility to warn women of the association. "We now have data that suggest there's an association between the Zika virus and microcephaly," she said. And even though scientists don't know how the virus causes the disease, "people aren't waiting. … People are out there saying, 'Oh my gosh, be aware, this is trouble.'"

J&J and Imerys, the talc supplier, argue that the statistical associations between use of the powder and ovarian cancer are limited, weak, and based on unreliable data. They say a causal link isn't biologically plausible, because there's no proof that talc particles can move up through the reproductive tract or that once there they could cause cancer. And if there's no causal connection, they say there's no reason to add a warning to Baby Powder. "There are statistical correlations. You can always calculate correlations," says Joshua Muscat, a professor of public health sciences at Penn State College of Medicine who serves as an expert consultant to J&J. "There hasn't been a single scientific body that has considered talc to be a causal agent. Many don't even consider talc to be a risk factor. To me, the science is black and white."

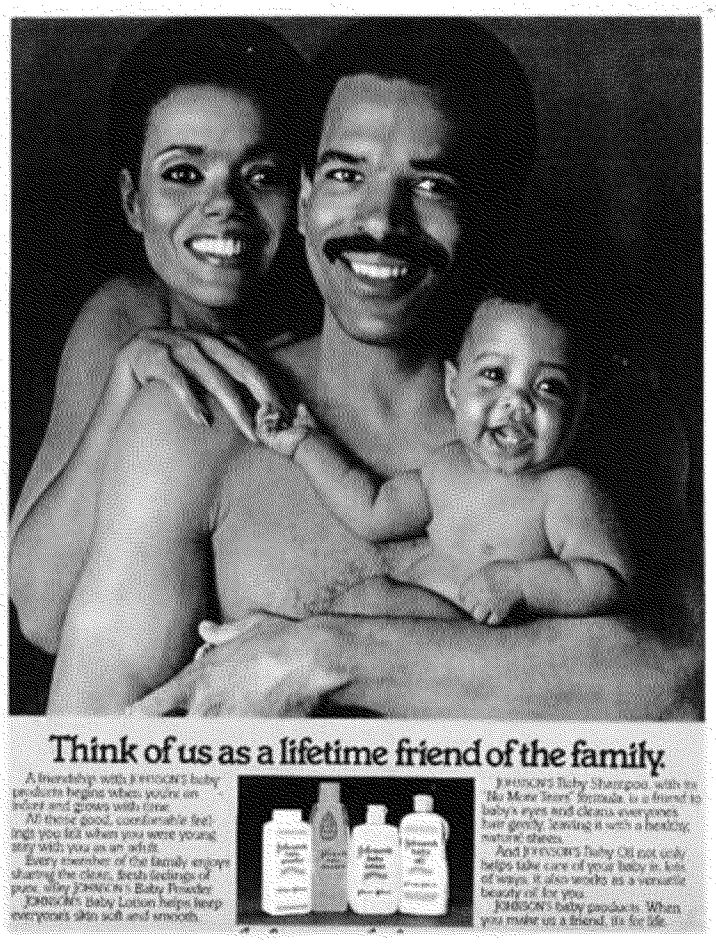
The odds of a woman in the U.S. falling ill with ovarian cancer are 1 in 70. Talc use is associated with worse odds, 1 in 53, according to those epidemiological studies. The risks seem to be higher for invasive serous cancer, which Fox had. Ovarian cancer is among the most deadly cancers. Some 20,000 women are diagnosed each year, often after the disease has spread. The symptoms are easily dismissed as menstrual or abdominal discomfort. There's no regular screening for ovarian cancer, no known causes, only risk factors, and some research suggests the malignancy may begin outside the ovaries, at the end of the fallopian tubes. More than 14,000 women die from the disease every year.

At the Fox trial, Ness did some harsh math for the jury. She claimed that Baby Powder use could contribute to some 2,500 women being diagnosed with ovarian cancer every year and 1,500 dying. The defense counsel, with great skepticism, called that figure "astonishing." Ness also noted that although black women generally have lower odds than white women of getting ovarian cancer, a small study recently showed they're more at risk of developing ovarian cancer

when exposed to talc.

In the last months of her life, Fox answered questions from attorneys on both sides of the case. The audio of her deposition was played in the courtroom near the end of the three-week trial. When asked why she was suing J&J, she said, "To put out there that we as women got to take care of ourselves. This is a disease I didn't ask for. But who am I? I just want to do right."

The science may be limited, and it may be ambiguous. Many of the researchers involved, including Cramer, say more study is necessary. But the science wasn't on trial in St. Louis; Johnson & Johnson was. "You don't win with jurors on science. They don't understand science, statistics, the design of studies," says Erik Gordon, a professor at the School of Business and School of Law at the University of Michigan. "They do understand there was some evidence of a connection between talc and cancer, and J&J didn't tell customers about it."



J&J ads from 1965 and 1980.

Ebony magazone ad: Gaslight Ad Archives

Lawyers for Fox introduced documents from 1986 through 2004 that, however selective they may be, portray a company struggling to revive interest in a symbolically important product with no proven health benefits and some suspected health risks. A 1992 memo outlining "major opportunities and major obstacles" acknowledged that "negative publicity from the health community on talc (inhalation, dust, negative doctor endorsement, cancer linkage) continues." The same memo included a recommendation to "investigate ethnic (African-American, Hispanic) opportunities to grow the franchise," noting that these women accounted for a high proportion of sales. An added handwritten note says the company planned a print advertising campaign. Goodrich, the J&J spokeswoman, said in her e-mail that this was "simply part of the company's efforts to appropriately understand who is using its products." More than a decade later, a task force devoted to improving sales of Shower to Shower, a mix of talc and cornstarch marketed to women, concluded: "African American consumers in particular will be a good target with more of an emotional feeling and talk about reunions among friends, etc., team up with *Ebony* Magazine." It suggested promotions in churches, beauty salons, and barbershops, and Patti LaBelle or Aretha Franklin as celebrity endorsers. Neither became a spokeswoman for the brand. It's not clear how much of the rest of the plan was put into action, since the company had already been advertising to blacks.

It's standard practice for companies to focus on their most committed customers. Airlines take care of business fliers; loyal shoppers get special deals at stores. "That's probably what they were doing," says Hennessy, the Kellogg marketing professor. "In today's climate, though, that looks horrible. From the outside it looks like J&J is less concerned, not more concerned, about its most loyal users because of their ethnic origin."

Baby Powder is a legacy brand in the black community. "Some people might say, 'What's wrong with companies recognizing women of color as important consumers?' " says Robin Means Coleman, a professor of communications studies and Afro-American Studies at the University of Michigan. "We do want that. But we do not want companies to market potentially carcinogenic products."

Salter, Fox's son, hadn't been aware of the marketing documents until the trial. "When I heard about it, I was infuriated," he says. "And so was the jury."

In the 1990s a toxicologist named Alfred Wehner worked as an outside consultant for J&J. His official role was to help evaluate the research on ovarian cancer and talc and advise the company on its response. Unofficially, he was its scold. Wehner was on J&J's side, but he was concerned that a cosmetics trade group (partly funded by the company) was mischaracterizing the scientific case

for talc. “A true friend is not he who beguiles you with flattery but he who discloses to you your mistakes before your enemies discover them,” Wehner began a 1997 letter to Michael Chudkowski, J&J’s manager of preclinical toxicology. Wehner described statements on talc research from the group as inept, misleading, and outright false. Referring to a statement a few years earlier, he wrote: “At that time there had been about 9 studies (more by now) published in the open literature that did show a statistically significant association between hygienic talc use and ovarian cancer. Anybody who denies this risks that the talc industry will be perceived by the public like it perceives the cigarette industry: denying the obvious in the face of all evidence to the contrary.” He wanted the trade group to argue that the studies’ biological significance was questionable.

Cosmetic talc isn’t a big part of Imerys’s business. The company, formerly called Luzenac, primarily sells the mineral for industrial purposes. But until 2006, it also fought any suggestion that talc could be a potential carcinogen. In the late 1990s, according to a Luzenac memo introduced at the trial, executives visited the head of epidemiology at the University of California at Irvine for advice on how “to stop the rumor about Ovarian cancer.” One suggestion: Get “two or three experts from the club” to make the scientific case. “The club” could refer to independent scientists Luzenac had worked with before, but Fox’s lawyers argued for a more sinister interpretation—that these were scientists who would respond to industry pressure. They also suggested that Luzenac and J&J exerted influence over a government group. In 2000 scientists with the National Toxicology Program, part of the U.S. Department of Health and Human Services, voted 13-2 to list talc, used perineally, as a possible human carcinogen, according to Fox’s lawyers, but the companies persuaded the NTP to defer an official decision on the status of talc. A Luzenac executive, Richard Zazenski, wrote to a colleague afterward: “We, the talc industry, dodged a bullet in December, based entirely over the confusion of the definition issue.” He was referring to ambiguity over the composition of the talc studied because, until the early 1970s, some powder contained naturally occurring asbestos fibers. He also discussed a coming NTP review, saying, “Time to come up with more confusion!” Imerys declined to comment on the specifics of the trial, but one witness for the defense offered the possibility that Zazenski was joking. Goodrich, the J&J spokeswoman, said any suggestion by Fox’s lawyers of improper influence is “merely an unsubstantiated allegation.”

In 2006, the IARC, the WHO cancer agency, declared that perineal use of cosmetic-grade talc was possibly carcinogenic. It cited “a modest, but unusually consistent, excess in risk” and also noted that bias in the studies couldn’t be ruled out. Publicly, Luzenac and J&J tried to diminish the significance of the designation; red meat and coffee are also included in this group of possible carcinogens.

Before the year ended, however, Luzenac stopped backing studies to prove talc's safety because the "horse has already left the barn," wrote one executive, noting that cosmetic companies had also cut funding. One of their primary arguments for doing so, he said, was that there were already too many studies showing an association with ovarian cancer "to stem the tide of negative sentiment." More important, Luzenac added a warning on the safety data sheet included with the 2,000-pound bags of talc it delivers to J&J: Perineal use of the powder is a possible risk factor for ovarian cancer.

"We, the talc industry, dodged a bullet in December. ... Time to come up with more confusion!"

Johnson & Johnson says it will continue to defend the safety of talc, and it does so on its website. There, in a section explaining its policies about ingredients, the company addresses concerns over formaldehyde, parabens, phthalates, and triclosan—chemicals with damaged reputations, and worse. In every case, J&J states that the chemicals haven't been proven harmful or that they were used in small enough amounts to be safe, but the company decided to remove them from its productsanyway. "We understand that from your perspective, government regulations may not be your only consideration when it comes to the personal-care products you and your family use," it says about parabens. For phthalates, the company says it recognizes that "the best way to keep your confidence was not to use it at all."

Why not apply that same standard to talc? Goodrich said the company listens when consumers raise concerns about ingredients. But "few ingredients have the same demonstrated performance, mildness and safety profile as cosmetic talc."

The first woman to sue Johnson & Johnson for not warning of the risks of talcum powder was Deane Berg, who was diagnosed with ovarian cancer in 2007. She says she turned down a $1.3 million out-of-court settlement because she didn't want to sign a confidentiality clause. Her case went to trial in 2013 in a South Dakota federal court as she was in remission. The jury found J&J was negligent, but didn't award Berg any damages.

After the Fox verdict, 17,000 people contacted her attorneys at Beasley Allen; the firm is looking into 2,000 of those, in addition to 5,000 potential claims it was already investigating. Its next case will be tried in the same St. Louis circuit court

as Fox's, which has a reputation for being sympathetic to plaintiffs. Gloria Ristesund's trial is set for April. She used Baby Powder for 40 years and was diagnosed with ovarian cancer in 2011.

Among those waiting their turn is Tenesha Farrar, who was diagnosed with Stage 3 ovarian cancer in 2013 and is represented by the Lanier Law Firm. Farrar, who's 40 and black, says she'd used Baby Powder and Shower to Shower (which J&J sold to Valeant in 2012) for the last two decades. "My grandmother and mother used it, and I learned from them," she says. After hearing about the J&J marketing document, she began crying. "I can't believe they singled us out." Farrar had chemotherapy and a full hysterectomy. She had to take off five months from her work as a clerk in a dialysis clinic outside St. Louis. She lost her health insurance because she exceeded the policy limits and had to skip her last chemo treatment. She and her husband eventually filed for bankruptcy. She's back at work now. "I have five children who depend on me," she says. "I will never use another J&J product again."

(Corrects the year that the Ebony *magazine J&J ad ran.)*

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National Center for Environmental Assessment

Office of Research and Development, U.S. EPA

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To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Tue 3/8/2016 10:39:56 AM
Subject: FW: Le Monde
Le Monde 7 mars 2016.pdf

Dear Vincent,
I hope you are well. Thought you might find of interest the latest news on glyphosate in the EU in the attached (in French) or via these links (in English):
http://www.theguardian.com/environment/2016/mar/04/eu-states-rebel-against-plans-to-relicense-weedkiller-glyphosate
http://www.reuters.com/article/us-health-eu-glyphosate-idUSKCN0W922K
Bonne journée,
Kate

Bataille sur l'avenir du glyphosate en Europe

La volonté de la Commission européenne de renouveler l'autorisation de l'herbicide se heurte à une forte o

Votera, votera pas ? La Commission européenne espérait expédier l'affaire sans fracas et faire adopter par les Etats membres, au cours de la réunion du Comité permanent des végétaux, des animaux, des denrées alimentaires et de l'alimentation animale, prévue lundi 7 et mardi 8 mars, un renouvellement de l'autorisation du glyphosate, celle-ci expirant fin juin en Europe. Dans un projet de décision, dont *Le Monde* a obtenu copie, Bruxelles prévoyait une remise en selle de ce désherbant – principe actif du célèbre Roundup de Monsanto – jusqu'en 2031.

Mais la semaine écoulée a vu la polémique s'intensifier sur la dangerosité de cette substance, la plus utilisée au monde, et contrarier les projets de Bruxelles. Au point que nul ne semble savoir si la réunion des 7 et 8 mars scellera, ou non, l'avenir de l'herbicide. *« Ce qui est sûr, c'est qu'il y aura discussion sur le glyphosate* [les 7 et 8 mars en comité], dit un porte-parole de l'exécutif européen. *Mais nous ne sommes pas sûrs que le vote se tiendra. »*

La Commission s'appuie sur l'Autorité européenne de sécurité des aliments (EFSA). Celle-ci, dans un avis rendu le 12 novembre 2015, estime *« improbable »* que le glyphosate soit cancérogène pour l'homme. Les demandes d'interdiction du produit reposent, elles, sur un autre avis, diamétralement opposé, rendu en mars 2015 par le Centre international de recherche sur le cancer (CIRC) – l'agence de l'Organisation mondiale de la santé (OMS). Pour le CIRC, le glyphosate est un *« cancérogène probable pour l'homme »*, mutagène (toxique pour l'ADN) et cancérogène pour l'animal.

Mobilisation de la société civile

Devant ce désaccord, ce sont d'abord des députés européens qui ont demandé le report de la décision. A Strasbourg, quatre groupes parlementaires de gauche ont écrit, le 3 mars, au commissaire européen à la santé, Vytenis Andriukaitis, lui demandant de *« reporter toute décision, au moins jusqu'à ce que le Parlement européen prenne une position formelle sur le sujet »* , après *« un examen approfondi »* du dossier. Le lendemain, la ministre française de l'environnement, Ségolène Royal, surprenait tous les observateurs en annonçant que la France s'opposerait à la proposition de Bruxelles. *« La décision proposée est une nouvelle autorisation pour quinze ans*, dit Mme Royal au *Monde*. *La France s'alignera sur la Suède pour dire non. »* Les Pays-Bas ont de leur côté annoncé que si le vote était maintenu les 7 et 8 mars, ils voteraient contre le renouvellement.

« La décision proposée est une autorisation pour quinze ans. La France s'alignera sur la Suède pour dire non »

SÉGOLÈNE ROYAL
ministre de l'environnement

Ces réticences font suite à une intense mobilisation de la société civile. Des pétitions lancées par les organisations non gouvernementales (ONG) Avaaz et Greenpeace, demandant l'interdiction du glyphosate, ont rassemblé plus d'un million et demi de signatures. En France, des associations traditionnellement peu engagées dans la lutte pour la protection de l'environnement, comme la Ligue contre le cancer, ont également appelé à la fin du glyphosate. D'autres ONG européennes – les Amis de la Terre, Générations futures, Pesticide Action Network, etc. – ont annoncé le 3 mars le dépôt d'une plainte devant un tribunal viennois contre l'EFSA et la vingtaine d'industriels commercialisant des pesticides contenant du glyphosate pour *« fraude réglementaire »* et détournement des procédures en vigueur pour l'évaluation du risque.

La discorde entre l'EFSA et le CIRC a conduit de nombreux scientifiques à examiner le dossier en détail. Pour une part, les divergences s'expliquent par les méthodologies des deux organismes. L'EFSA a pris en compte les études réalisées par les industriels eux-mêmes, et tenues confidentielles. Au contraire, le CIRC n'a tenu compte que des études sur le sujet – environ un millier – publiées dans la littérature scientifique.

Le glyphosate entre dans la composition de plus de 750 produits phytosanitaires

Mais pour certains, la différence des corpus évalués par le CIRC et l'EFSA n'explique pas tout. Conduits par Christopher Portier, conseiller du CIRC, ancien directeur du National Center for Environmental Health américain et l'un des papes de la cancérogenèse, une centaine de toxicologues, d'épidémiologistes et de biologistes ont écrit fin novembre 2015 au commissaire européen à la santé, estimant l'avis de l'EFSA *« trompeur »* fondé sur une démarche *« scientifiquement inacceptable »*. Une virulence rare dans l'entre-soi des experts – réitérée dans un article publié le 3 mars par le *Journal of Epidemiology and Community Health*

Enjeux économiques

De leur côté, les industriels assurent que le glyphosate est sûr et qu'il est, dans tous les cas, moins problématique que les autres herbicides disponibles. Les enjeux économiques sont en outre considérables. Le glyphosate n'est pas seulement le principe actif du Roundup : selon les données colligées par l'OMS, il entre dans la composition de plus de 750 produits phytosanitaires, commercialisés par environ 90 fabricants répartis dans une vingtaine de pays.

De plus, il est la pierre angulaire de la stratégie de développement des biotechnologies, la grande majorité des plantes transgéniques étant modifiées pour le tolérer et rendre ainsi plus simple son épandage. Ces dernières années, l'adoption rapide des cultures OGM dites « Roundup Ready » (résistantes au Roundup) et apparentées a tiré vers le haut la production mondiale de glyphosate : de 600 000 tonnes en 2008, elle atteignait 720 000 tonnes en 2012.

Au-delà d'une controverse sur la dangerosité d'un pesticide, l'affaire cristallise la crise de confiance actuelle dans le système européen d'évaluation et de gestion des risques sanitaires et environnementaux. La Commission a ainsi été condamnée le 16 décembre 2015 par le Tribunal de l'Union européenne pour son inaction sur le dossier des perturbateurs endocriniens. Deux mois plus tard, le médiateur européen, dans une décision sévère, fustigeait le laxisme bruxellois en matière d'autorisation des pesticides. Mme Royal et M. Andriukaitis en ont d'ailleurs convenu lors d'une récente entrevue : il faut changer les règles de fonctionnement du système.

stéphane foucart

LES DATES

2015

20 mars Le Centre international de recherche sur le cancer, une agence de l'Organisation mondiale de la santé, classe le glyphosate *« cancérogène probable pour l'homme »*.

12 novembre L'Autorité européenne de sécurité des aliments (EFSA) estime *« improbable »* le potentiel cancérogène du glyphosate.

27 novembre Une centaine de scientifiques écrivent à la Commission européenne pour protester contre l'avis de l'EFSA.

2016

18 février Le médiateur européen dénonce le laxisme de Bruxelles dans les autorisations de mise sur le marché des pesticides.

7 et 8 mars Réunion du Comité permanent de la chaîne alimentaire et des denrées animales, avec le glyphosate à l'ordre du jour

Paris se prépare à la « crue du siècle »

La capitale organise, du 7 au 18 mars, une vaste simulation de gestion d'une inondation identique à celle de 1910

Dans les prochaines heures, la hauteur de la Seine au pont d'Austerlitz, à Paris, est susceptible de passer au-delà de 7,2 m. Circulation normale sur les réseaux TER, mais trafic interrompu sur la ligne C du RER et fortement perturbé sur les lignes A et B. Nombreux tronçons routiers et ponts impraticables ou inaccessibles en Essonne, en Seine-et-Marne et en Seine-Saint-Denis. Hôpitaux de Créteil et de Villeneuve-Saint-Georges (Val-de-Marne) privés d'électricité. Centre d'incinération d'Issy-les-Moulineaux (Hauts-de-Seine) hors d'usage, les collectes de déchets ménagers doivent être détournées…

A la Préfecture de police de Paris, dans les communes bordant la Seine et la Marne, chez les opérateurs téléphoniques, dans les hôpitaux…partout, depuis ce lundi 7 mars, au rythme des bulletins de situation diffusés au fil de la montée des eaux, l'effervescence s'accroît pour limiter les dégâts, maintenir l'activité des services vitaux et organiser la protection des Franciliens.

C'est au scénario catastrophe d'une crue centennale identique ou supérieure à la grande crue de 1910 que Paris se prépare. Du 7 au 18 mars, avec le soutien de l'Union européenne, la Préfecture de police organise un exercice grandeur nature de gestion de crise, baptisé « EU Sequana 2016 ».

Une opération hors norme à laquelle prendront part 87 institutions et entreprises (Assistance publique-Hôpitaux de Paris, EDF, RATP, SNCF, Orange, Veolia…), mais aussi six communes, l'ensemble des ministères et l'armée. Elle mobilisera dans cinq départements 150 policiers et 900 sauveteurs, dont certains viendront d'Italie, d'Espagne, de Belgique et de République tchèque.

La crue centennale affectera près de 5 millions d'habitants d'Ile-de-France

Certes, il ne s'agit que de simulation, pour l'instant. Aujourd'hui, si la population ne veut y croire, le scénario d'une crue centennale de la Seine se reproduira, c'est une certitude. Une telle crue affectera directement ou indirectement près de 5 millions d'habitants d'Ile-de-France, dont 500 000 à évacuer, et pourrait causer, selon un diagnostic publié au début de 2014 par l'Organisation de coopération et de développement économiques, jusqu'à 30 milliards d'euros de dommages directs. La seule incertitude : quand cela arrivera-t-il ?

Beaucoup d'imprévus

« Hors attentat, le risque d'inondation constitue le premier risque majeur susceptible d'affecter l'Ile-de-France. Car il concerne tous les réseaux structurants : eau, transports, santé, énergie, téléphone, électricité…» rappelle-t-on au secrétariat général de la zone de défense de la Préfecture de police, qui tient à préciser que les scénarios de l'exercice, pour bluffant de réalisme qu'ils soient, ne sont que des hypothèses de travail. Il n'est pas possible, en effet, de tout anticiper et planifier, un tel événement naturel comportant beaucoup d'imprévus.

La simulation consistera essentiellement en un exercice sur table, l'ensemble des acteurs communiquant entre eux via un logiciel partagé de gestion de crise. Le scénario de l'exercice, qui rythmera l'activité des différentes cellules de crise, a néanmoins été élaboré à partir de faits réels et suivra une montée des eaux de la Seine, de la Marne et de l'Yonne, au rythme de 50 centimètres puis 1 mètre par jour, pour atteindre un territoire de 500 km² sous les eaux.

Ce faisant, des opérations concrètes de terrain (opération de dépollution, évacuation d'une maison de retraite, sauvetage d'une péniche…) sont aussi prévues sur différents sites en Ile-de-France au cours du week-end des 12 et 13 mars, au moment du pic de crue théorique. *« L'objectif majeur de Sequana est de tester la capacité de réaction des différents opérateurs, et surtout à se coordonner,* explique le préfet de police, Michel Cadot. *Car si la plupart ont conçu un plan de continuité d'activité en cas de crue, l'interdépendance de tous ces plans n'a jamais été travaillée. Cette capacité sera éprouvée en phase de crue comme en phase de décrue, de retour à la normale. »*

L'exercice a aussi pour vocation de sensibiliser les populations au risque d'inondation. *« L'objet n'est pas de créer de l'anxiété*, précise Michel Cadot, *mais de favoriser une prise de conscience du risque, d'inciter les habitants à prendre la mesure des conséquences d'une crue majeure et s'y préparer. »* Au cours du week-end des 12 et 13 mars, le public pourra ainsi assister aux différentes manœuvres réelles. Et un site d'information sera aménagé sur le Champ-de-Mars, où un film en 3D de simulation d'inondation sera diffusé et des ateliers et des jeux permettront de tester sa vulnérabilité à la crue.

laetitia van eeckhout

To: Cogliano, Vincent[cogliano.vincent@epa.gov]; Ross, Mary[Ross.Mary@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Bussard, David[Bussard.David@epa.gov]; Gatchett, Annette[Gatchett.Annette@epa.gov]
From: Vandenberg, John
Sent: Mon 3/7/2016 5:43:49 PM
Subject: Fwd: Cancer and the most widely used pesticide

FYI .

Sent from my iPhone

Begin forwarded message:

From: Kathy Burns <kmb@sciencecorps.org>
Date: March 4, 2016 at 1:24:26 PM EST
To: <olden.kenneth@epa.gov>
Cc: 'John Vandenberg' <vandenberg.john@epa.gov>
Subject: Cancer and the most widely used pesticide

Hi Ken,
Even though your office doesn't specifically address pesticides, I thought you would want to see this article that many of us worked on to counter intense political pressure regarding the determination that the world's most widely used pesticide is a carcinogen.

"Commentaries: Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)" (3 Mar 2016)
(Full text access via the link below.)

It is extremely difficult these days for government agencies to tell a scientific truth that is unpalatable to industry or other agencies. But it is what separates public servants from those who would enable the status quo to supersede the public good.

Have a good weekend.
Kathy

-----Original Message-----
From: Chris Portier [mailto:cportier@me.com]
Sent: Friday, March 4, 2016 12:21 AM
To: Dr. Christopher Portier <cportier@mac.com>
Subject: JECH paper is online. Please share it.

http://jech.bmj.com/content/early/2016/03/03/jech-2015-207005.full

To: Cogliano, Vincent[cogliano.vincent@epa.gov]; Robert Baan[BaanR@visitors.iarc.fr]
Cc: dkrewski@uottawa.ca[dkrewski@uottawa.ca];
Ex. 6 - Personal Privacy
From: Kurt Straif
Sent: Thur 2/18/2016 10:05:05 PM
Subject: RE: Jane's Table X, detailed (contd.)

Dear Vicent,

Pls see my insert below,

Kurt

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: 17 February 2016 00:30
To: Kurt Straif <StraifK@iarc.fr>; Robert Baan <BaanR@visitors.iarc.fr>
Cc: dkrewski@uottawa.ca; Ex. 6 - Personal Privacy
Subject: RE: Jane's Table X, detailed (contd.)

Hello everyone—Thank you all for moving this forward. I agree with Robert's and Kurt's comments and corrections (except that I remember that TCDD was a mechanistic upgrade in v69 but not in v100F, though the "site" was all cancers combined).

This is correct, so this shows that we must be clear what and how we count: do we count what has ever been a mechanistic upgrade any time in history (independent what happened thereafter), or do we count on the basis of the current evaluation?

Attached is what I see as a simplification of the previous table X. This one is more compact and may also be more intuitive to those who like Venn diagrams. For each row, the left-hand circle would encompass the second and third columns, the right-hand circle the third and fourth columns, with the third column constituting the overlap.

The only information I dropped from table X was the column on limited evidence in humans. I don't remember a decision to include this information, and for the subset of cancer sites covered in table X, it provides no useful insights, at least to me.

I can't resist pointing out that another way of indicating which agents were sufficient in humans, in animals, or in both is a heat map, but I don't want to go back one month.

Best regards to everyone,

Vincent

From: Kurt Straif [mailto:StraifK@iarc.fr]
Sent: Wednesday, February 10, 2016 9:12 AM
To: Robert Baan <BaanR@visitors.iarc.fr>
Cc: dkrewski@uottawa.ca; Cogliano, Vincent <cogliano.vincent@epa.gov>;
Ex. 6 - Personal Privacy
Subject: RE: Jane's Table X, detailed (contd.)

Robert,

Given the rarity of cancers of nasal cavities I would assume that all of these studies have essentially looked at all combined nasal cavities, but may have used different terminology in their papers, or the WG may have chosen different terminology. This is more likely than different site-specific evidence for the different agents, but this assumption would need to be verified.

Below is the ICD9 classification pertaining to this group of cancers. If 160.1 was indeed excluded (like salivary gland often being excluded from oral cavity) the best name for this group of cancers would be "Malignant neoplasm of nasal cavities and accessory sinuses"

Kurt

160 Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses

160.0 Nasal cavities

Cartilage of nose Septum of nose

Conchae, nasal Vestibule of nose

Internal nose

Excludes: nasal bone (170.0)

nose NOS (195.0)

olfactory bulb (192.0)

posterior margin of septum and choanae (147.3)

skin of nose (172.3, 173.3)

160.1 Auditory tube, middle ear, and mastoid air cells

Antrum tympanicum Tympanic cavity

Eustachian tube

Excludes: auricular canal (external) (172.2, 173.2)

bone of ear (meatus) (170.0)

cartilage of ear (171.0)

ear (external) (skin) (172.2, 173.2)

160.2 Maxillary sinus

Antrum (Highmore) (maxillary)

160.3 Ethmoidal sinus

160.4 Frontal sinus

160.5 Sphenoidal sinus

160.8 Other [see Note 3 at beginning of Chapter II]

160.9 Accessory sinus, unspecified

From: Robert Baan
Sent: 10 February 2016 12:08
To: Kurt Straif <StraifK@iarc.fr>
Cc: Daniel Krewski <dkrewski@uottawa.ca>; Cogliano.Vincent@epamail.epa.gov;
Ex. 6 - Personal Privacy
Subject: Jane's Table X, detailed (contd.)

Thank you, Kurt, for your quick reply and useful corrections.

I added my responses in the margin (see attachment).

A few additional points: we may consider indicating all the mechanistic upgrades with a footnote; we should perhaps clarify the terms pharynx and oro/naso/hypopharynx; is 'nasal sinus' meant to be the same as 'paranasal sinus(es)'?

Best regards to all,

Robert

From: Kurt Straif
Sent: Wednesday, February 10, 2016 10:55 AM
To: Robert Baan; Daniel Krewski; Cogliano.Vincent@epamail.epa.gov
Cc: Ex. 6 - Personal Privacy
Subject: RE: Jane's Table X, detailed

Dear Robert and all,

Attached are my comments.

Thank you,

Kurt

From: Robert Baan
Sent: 10 February 2016 01:22
To: Daniel Krewski <dkrewski@uottawa.ca>; Cogliano.Vincent@epamail.epa.gov
Cc: Kurt Straif <StraifK@iarc.fr>; **Ex. 6 - Personal Privacy**
Subject: Jane's Table X, detailed

Dear all,

Further to Ron's comments about Jane's Table X ('this Table gives numbers of agents and does not say what they are') I have prepared the attached Table for the different sites in the upper aerodigestive system, in which this information is now included. For example, under 'nasopharynx' the numbers 5 (humans) and 1 (rodents) in Jane's Table X are now identified. However, in some cases Jane's numbers do not completely fit with my Table (to be double-checked). Agents with exact concordance are indicated in red. I guess these would represent the 'overlap' in the additional column that Vincent had proposed.

Before I continue, I value your thoughts.

Best wishes,

Robert

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To: Kathryn Guyton[GuytonK@iarc.fr]; Dana Loomis[LoomisD@iarc.fr]; Nicolas Gaudin[GaudinN@iarc.fr]; Véronique Terrasse[TerrasseV@iarc.fr]
Cc: Chris Portier[cportier@me.com]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kurt Straif
Sent: Sun 2/14/2016 3:22:17 PM
Subject: RE: IARC and vinyl chloride- skewed epidemiology news

Dear all,

Thanks to Vincent and Chris for alerting us to this story from CSPI.

While I agree with the principle concern that "The dominance of industry-funded research for specific chemicals has

become more common", and while I have not had the time to look into the specific criticism wrt the industry-sponsored study, I wanted to note a few issues:

"in 1979, the International Agency for Research on Cancer, or IARC, part of the World Health Organization, took the unequivocal position that vinyl chloride caused brain tumors"

This is only in the appendix to supplement 1 and as such does not constitute an official evaluation by the WG. There are other associations listed that are by current standards not considered as cancer site-specific sufficient evidence, eg VC and lung cancer.

"Citing that study [the industry-sponsored] and others, IARC in 2008 reversed itself."

Additional re-evaluations in suppl 4 and suppl 7 did not formally link VC with brain cancer. Like in the main body of suppl 1 the evaluation of "sufficient evidence", in line with the Preamble in effect at the time, pertains to cancer in humans in general. Section 5.2 of Vol 97 (the Monographs meeting that classified 1,3-butadiene as Group 1) summarized:

"The Working Group did not find strong epidemiological evidence for associations of

exposure to vinyl chloride with cancers of the brain or lymphatic and haematopoeitic

tissue or melanoma. Although the associations found for these cancers in specific studies

may reflect true increases in risk, the findings were inconsistent between studies, no clear exposure–response relationships were found in the European multicentric study and, for several of the sites, the numbers of observed and expected cases were small.

Vol 100F came essentially to the same conclusion wrt brain cancer.

Fyi, Vol 97 and 100F experts included Leslie Stayner, Paolo Vineis, Liz Ward; Manolis Kogevinas, Nat Rothman, Chris Portier and Harri Vainio, and I don't remember a controversial debate on brain cancer, while there was one for HCC, classified as "sufficient".

"Otto Wong, the now-retired author of one of the study updates, expressed concern after hearing the Center's findings."

Interesting…

"that workers' recollections of the potency of odors — categorized as high, medium or low — would be one way to estimate exposures. Jim Tarr, who worked as an air pollution regulator in Texas at the time, said such a method "doesn't even reach the level of being junk science"

That same method of exposure assessment (as well as several other methods) was also employed by the European pooled analysis performed by Liz Ward, who was at IARC at the time, and showed an increased risk of haemangiosarcoma of the liver.

I think what is needed is the possibility for critical re-analysis of industry-sponsored studies by independent researchers – much more than the re-analysis of US-NCI studies by industry, or even better, requirement for independent funding and conduct of such studies in the first place. One of the next steps in VC-brain cancer debate should be a letter to the editor once the industry study is published.

Bon WE

Kurt

From: Chris Portier [mailto:cportier@me.com]
Sent: 12 February 2016 19:09
To: Kurt Straif <StraifK@iarc.fr>; Kathryn Guyton <GuytonK@iarc.fr>
Subject: Fwd: IARC and vinyl chloride- skewed epidemiology news

Begin forwarded message:

From: Kathy Burns <kmb@sciencecorps.org>

Subject: IARC and vinyl chloride- skewed epidemiology news

Date: February 11, 2016 at 12:03:44 PM PST

To: Chris Portier <cportier@me.com>

Cc: 'Ron Melnick' <Ex. 6 - Personal Privacy>, James Huff <huff1@niehs.nih.gov>

Hi Chris,

I assume you've seen the story below that came out yesterday - another very good investigative piece from the Pulitzer Prize winning Center for Public Integrity. I think it is important to pass this along to IARC with a request that they read it carefully and quickly reconsider their actions on the vinyl chloride cancer classification. Given your work on glyphosate with respect to the defense of IARC's decisions, I thought you might want to communicate with them about this.

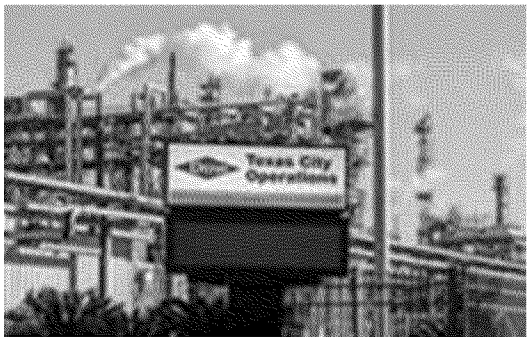
Kathy

Science for Sale

Making a cancer cluster disappear

After a record number of brain tumors at a chemical plant, industry launched a flawed study that obscured the extent of the problem

By David Heath email



Science and opinion have become increasingly conflated, in large part because of corporate influence. As we explain in "Science for Sale," an investigative series by the Center for Public Integrity and co-published with Vice.com, industry-backed research has exploded — often with the aim of obscuring the truth — as government-funded science dwindles.

TEXAS CITY, Texas — It began with a headache; then came shaking of the hands. Leuvell Malone's wife noticed unusual behavior. He struggled to button his shirt straight and crashed the car into the hot-water heater in the garage. Finally, a seizure landed the 55-year-old chemical worker in the hospital. His doctor at first thought Malone might have suffered a stroke. But it turned out to be worse than that. The father of four had a rare and deadly brain tumor.

During his 32 years of greasing machines at the sprawling Union Carbide plant south of Houston, Malone feared the chemicals he breathed might one day make him sick, his sons recall. So he reported his illness to the local office of the U.S. Occupational Safety and Health Administration.

That was in November 1978. Just a few days later, Bobby Hinson, one of Malone's co-workers, died of the same rare tumor, known as glioblastoma. He was 49 years old. OSHA inspectors went to the plant to find out how many other workers there had died of brain cancer.

To their surprise, the plant's medical director already had compiled a list of 10 names. "To walk in the front door without tracing through the population and come up with 10 brain cancers is just startling," an OSHA investigator, Dr. Victor Alexander, told a local reporter. Malone would die just three months after he was diagnosed.

More than 7,500 men had worked at the plant since it opened in 1941. Tracking those who had died was a daunting task. It took three years, but scientists at OSHA and their brethren at the National Institute for Occupational Safety and Health, or NIOSH, would discover 23 brain-tumor deaths there — double the normal rate. It was the largest cluster of work-related brain tumors ever reported, and it became national news, catching the attention of The Washington Post, The New York Times and even Walter Cronkite.

Gulf Plants Combed for Carcinogens

The Washington Post on February 19, 1979.

The leading suspect was vinyl chloride, a chemical used to make polyvinyl chloride plastic. PVC is found in an endless array of products from plastic wrap to vinyl siding to children's toys. Industry studies already had found higher-than-expected rates of brain cancer at vinyl chloride plants, and in 1979, the International Agency for Research on Cancer, or IARC, part of the World Health Organization, took the unequivocal position that vinyl chloride caused brain tumors.

Yet today, a generation later, the scientific literature largely exonerates vinyl chloride. A 2000 industry review of brain cancer deaths at vinyl chloride plants found that the chemical's link to brain cancer "remains unclear." Citing that study and others, IARC in 2008 reversed itself.

However, a Center for Public Integrity review of thousands of once-confidential documents shows that the industry study cited by IARC was flawed, if not rigged. Although that study was supposed to tally all brain cancer deaths of workers exposed to vinyl chloride, Union Carbide didn't include Malone's death. In fact, the company counted only one of the 23 brain-tumor deaths in Texas City.

The Center's investigation found that because of the way industry officials designed the study, it left out workers known to have been exposed to vinyl chloride, including some who had died of brain tumors. Excluding even a few deaths caused by a rare disease can dramatically change the results of a study.

Asked hypothetically what it would mean if deaths were left out, James J. Collins, the former director of epidemiology at Dow Chemical, which merged with Union Carbide in 2001, said, "That wouldn't make very good science."

Richard Lemen, a former U.S. assistant surgeon general and NIOSH deputy director, put it more bluntly: "I think that borders on criminal."

The vinyl chloride episode shows what can happen when scientific research is left to companies with a huge stake in its outcome. After launching a flurry of vinyl chloride studies in the late 1970s, OSHA and NIOSH abruptly stopped under the anti-regulatory climate instilled by the Reagan administration. The chemical industry, meanwhile, continued to update its studies and use them to defend against lawsuits by people blaming their brain cancers on vinyl chloride. The result was biased research that changed the scientific consensus. The final update of the largest vinyl chloride study is expected to be published this year.

The dominance of industry-funded research for specific chemicals has become more common as funding for biological research from the National Institutes of Health has become scarcer — declining 23 percent, adjusted for inflation, since 2003, according to the Federation of American Societies for Experimental Biology. In contrast, industry has shown a willingness to spend lavishly on research used in litigation.

The means regulators and courts sometimes must rely on scientific research paid for by companies with a huge financial stake in its outcome.

In a brief statement to the Center, the American Chemistry Council, the trade and lobby group that paid for the industry study, noted that the IARC determination that there is no association between vinyl chloride and brain cancer "was based on inconsistent findings among the available studies, lack of an exposure-response relationship, and small numbers of reported cases in most of the studies."

Otto Wong, the now-retired author of one of the study updates, expressed concern after hearing the Center's findings. If industry officials knew in advance that they were excluding the deaths of workers who may have been exposed, they should have designed the study differently, Wong said.

Ongoing environmental hazard

Despite stricter regulations on vinyl chloride in the workplace since 1975, the question of its health effects remains relevant. PVC plants in places such as Calvert City, Kentucky, and Plaquemine, Louisiana, still emit vinyl chloride into the air. In 2014, companies reported releasing more than 500,000 pounds of it, according to the U.S. Environmental Protection Agency. The EPA is expected to decide this year whether to set stricter emission limits for vinyl chloride and other chemicals discharged by PVC plants.

There have also been notable cases of vinyl chloride contamination. In 2012, a train derailment in Paulsboro, New Jersey, released heavy concentrations of the chemical into Mantua Creek, sending 250 people to the emergency room and stoking fears of long-term health effects. "I'm going to be worried for the rest of my life," said Alice Breeman, a mother of three who was caught in the release

and sued Conrail, CSX Transportation and Norfolk Southern Railway. CSX and Norfolk Southern have since been dismissed as defendants.

In 2014, residents of McCullom Lake, Illinois, settled an eight-year-old lawsuit in which they claimed exposure to vinyl chloride that bled into groundwater from a nearby chemical plant, now owned by Dow, had caused a cluster of 33 brain tumors. The village has just over 1,000 residents. Dow admitted no wrongdoing in the settlement, whose terms are confidential.

Today, all legal disputes and regulatory actions on vinyl chloride must rely heavily on industry studies given the dearth of independent research. An industry-sponsored update in 2000 — the largest and most-cited vinyl chloride study — reported 36 brain cancer deaths at 37 vinyl chloride plants among workers employed from 1942 to 1972. Despite the small number of cancers, that rate was 42 percent higher than what would have been expected in the general population.

By the slimmest of margins, however, the number of deaths failed to meet a standard known as statistical significance – at least a 95-percent certainty that the high rate of brain cancer was not simply a fluke. Even one more death could have altered that conclusion.

The Center was able to scrutinize how that study was designed and conducted after obtaining nearly 200,000 internal industry documents from lawyer William Baggett Jr. He spent nine years on a lawsuit filed by Elaine Ross, whose husband, Dan, worked at a vinyl-chloride plant in Lake Charles, Louisiana, and died from brain cancer in 1990 at the age of 46. The case was settled 15 years ago for several million dollars, Baggett said, adding that the exact terms were confidential.

Vinyl chloride first gained notoriety in 1974, when it was revealed that four workers at a B.F. Goodrich plant in Louisville had died of angiosarcoma of the liver, a cancer so rare that typically no more than 25 cases per year are reported in the United States. The most recent tally of liver angiosarcomas among people exposed to vinyl chloride is 197 worldwide, including 50 in the U.S.

The evidence of carcinogenicity in the Louisville case was so overwhelming that the plastics industry couldn't deny it. Still, the industry pushed back against new regulations, saying they could cost the nation up to 2.2 million jobs and cripple the plastics industry.

OSHA nonetheless went ahead in 1974 with a workplace limit for vinyl chloride that was 500 times stricter than the one in place when the Louisville cluster became public knowledge. The U.S. Food and Drug Administration banned the chemical from use in cosmetics and hair spray. Industry predictions of severe losses never came true. The regulations were met.

Built-in weaknesses

The vinyl chloride studies most often cited today — including a major study soon to be published — in fact are updates of a study first done in 1974. After companies learned of workers suffering from angiosarcoma, they quietly decided to find out what other cancers vinyl chloride might be causing.

The industry study was flawed from the start. The weaknesses built in to it only became worse as decisions were made on how to update it.

In June 1973, the industry's trade group, then known as the Manufacturing Chemists' Association, hired the consulting firm Tabershaw-Cooper Associates to tabulate cancers at vinyl-chloride plants. The first challenge was to compile a list of workers exposed. Rather than let scientists at Tabershaw-Cooper ultimately decide which workers should be put on the list, the chemical companies assigned the task to their own plant managers. At Union Carbide, managers decided to include only people working directly with vinyl chloride, based on some written records but also on supervisors' distant memories.

Until the mid-1970s, exposure data was crude to non-existent. The managers reasoned that workers' recollections of the potency of odors — categorized as high, medium or low — would be one way to estimate exposures. Jim Tarr, who worked as an air pollution regulator in Texas at the time, said such a method "doesn't even reach the level of being junk science."

Tarr, now an environmental consultant in Southern California, said it's ridiculous to expect anyone to remember distinct odors years after the fact. In fact, vinyl chloride can be smelled only at levels far higher than even the old regulations allowed.

Tabershaw-Cooper's final report — without revealing the methods used — said that measuring exposures at the plants "proved generally to be impossible." It acknowledged that managers' techniques for determining levels of exposure were "subjective" and had "questionable validity."

Even with this problematic data, Tabershaw-Cooper reported in 1974 that there were more brain tumors than expected at vinyl chloride plants. A follow-up completed in 1978 reported that brain cancers at vinyl-chloride plants were occurring at twice the normal rate.

There was evidence from the start that Union Carbide workers in Texas City who died of brain cancer had been exposed to vinyl chloride. When news of the first 10 brain cancers at the plant broke in 1979, Union Carbide's Gulf Coast medical director, Dr. David Glenn, acknowledged as much while also trying to deflect blame from the chemical.

"Although the press has strongly indicated that vinyl chloride may have been the culprit, only about one-half of our [brain cancer] cases had any known exposure to this chemical," he said in a statement.

Yet none of those workers was included in the study updates that have formed the bedrock of today's scientific consensus. The only brain cancer death from Texas City included in these updates was that of Luther Ott, a 57-year-old production worker who wasn't even diagnosed until a month after the medical director's statement. Ott died in February 1980.

Chemical industry officials knew before they hired Otto Wong to do an update that none of the 10 brain cancer deaths in Texas City had been included in previous studies, even though Glenn said half of the workers had been exposed to vinyl chloride.

One week after Glenn's statement, Union Carbide's corporate medical director, Dr. Mike Utidjian, told an industry task force that none of the 10 Texas City victims had a "clear cut" exposure. Nor were any included in previous studies.

Wong said it would have made more sense to start the study over rather than update a flawed one. "From the scientific point of view, a better approach would be to do a new study," he said. That would entail reanalyzing which workers were exposed and which weren't.

In fact, by March 1981, scientists at Union Carbide had determined that at least four of the workers who died of brain cancer had been exposed to vinyl chloride. The biostatistician who wrote that memo, Rob Schnatter, declined to comment for this story.

Schnatter did not keep the four dead workers a secret. He and another Union Carbide scientist acknowledged them in an article published in 1983. Schnatter wanted to amend which workers were in the industry study. In 1982 he sent a memo to his colleagues at Union Carbide, one of whom wrote a handwritten response : "No, we are not adding people to the cohort."

This reflected a critical decision that all but guaranteed the study's outcome. According to the protocol, workers included in the original study could be dropped from updates if new information showed they hadn't been exposed to vinyl chloride. But the reverse wasn't true. Workers not initially included in the study couldn't be added even if it turned out that they had been exposed, according to a Union Carbide memo.

In 1974, Tabershaw-Cooper was given a list of 431 exposed workers from Texas City. But when the study was updated a decade later, the number of exposed workers had dropped to 289 names. Susan Austin, a Union Carbide epidemiologist at the time, complained in an internal memo that the odd rules for reclassifying whether workers were exposed "could lead to substantial bias."

Collins, the former Dow epidemiologist, said it should been nearly impossible to cheat on this type of study. When scientists are deciding which workers were exposed to a chemical, they usually don't know which ones have died. Therefore, they can't skew the outcome by excluding dead workers. "There's no way to fudge the data," Collins said.

But in this situation, Union Carbide did know which workers had died. It also knew it was excluding workers who had been exposed to vinyl chloride. The Center found no evidence that Union Carbide removed workers with brain cancer who had been in the original 1974 study. But the documents show that when the study was updated, at least three brain-cancer victims Union Carbide knew had been exposed were not included. "It looks like they did leave them out by their own admission," said former NIOSH official Lemen, who at one time served as a consultant for lawyer Baggett.

Kenneth Mundt, the lead author of the most recent update of the vinyl chloride study and a principal at the consulting firm Ramboll Environ, at first promised to answer questions from the Center. But weeks later, Mundt said that the study's sponsor, the American Chemistry Council, wouldn't allow him to talk because of pending litigation.

A Dow spokesperson said, "If Texas City workers met the eligibility criteria … then they would have been included in the industry-wide study, regardless of the cause of death …. Not all Texas City workers had opportunity for exposure to vinyl chloride."

Leuvell Malone Jr. shows the only memento he has from his father, who died in 1979 from brain cancer. Malone worked at the Union Carbide vinyl chloride plant in Texas City, where 22 other workers died of the same rare cancer. But the company determined that he wasn't exposed to the chemical. "He was all over the plant," Malone Jr. said. "He had to be exposed."John Everett for the Center for Public Integrity

'Unusual' decisions

Documents show that more than three exposed workers might have been excluded from the updates. That's because of a decision made in the early 1970s not to include people who were not

stationed full-time in departments having direct contact with vinyl chloride. OSHA and NIOSH scientists noted that many of the brain cancer victims held jobs that would have brought them in contact with chemicals throughout the plant. They listed seven in maintenance, two in shipping and three in construction.

Leuvell Malone Sr. worked in maintenance. His son, Leuvell Malone Jr., said he had no idea Union Carbide claimed his father hadn't been exposed to vinyl chloride. "He was all over the plant. He did all of the oiling for all of the machinery," Malone said. "He had to be exposed."

The government study seems to back up Malone's claim. NIOSH reported in its study that "maintenance men moved throughout the plant and were exposed to many different agents in an irregular manner."

Richard Waxweiler, a former NIOSH epidemiologist involved in the investigation of the Texas City cancer cluster, said in a recent interview that he didn't know Union Carbide had excluded so many brain-tumor deaths from the industry study. He called it "unusual" that maintenance workers like Malone were left out.

Internal Union Carbide documents show that the company didn't dismiss the possibility that 10 other workers who died of brain cancer also may have been exposed to vinyl chloride. In fact, exposures may have been far more widespread. In the plant's own report to the Texas Air Control Board, which regulated air emissions at the time, Union Carbide said it released 940 tons of vinyl chloride into the air in 1975. That was after the company had implemented new pollution-control measures.

The Air Control Board calculated that in 1974, the Texas City plant released 3,000 tons of vinyl chloride — 12 times the emissions from all U.S. plants combined in 2014. Collins said the emissions data don't prove that everyone at the plant was exposed to vinyl chloride. But Tarr, who calculated the numbers at the time for the state of Texas, disagrees. "There's no question whatsoever that everyone who worked in that plant was exposed to vinyl chloride," he said. "It was only a question of, what was the amount of that exposure and what was the duration of that exposure?

"

Union Carbide strategized for nearly two years on how to limit the threat from government studies of the Texas City cancer cluster. One Union Carbide lawyer advised internally that the more brain cancer deaths there were, the easier it would be for widows like Leuvell Malone's wife, Ada, to win lawsuits.

The company decided to do its own analysis simultaneously, reasoning that "Independent investigations of the same set of data frequently yield differing results." The company also decided to hold a press conference to announce its results first, telling NIOSH just two days in advance. The

story was front-page news. "Our exhaustive studies neither indicate that any deaths due to brain cancer have been caused by occupational exposure, nor do they suggest any changes to our existing employee health programs or production procedures," plant manager Damon Engle said in a press release.

Union Carbide said only 12 employees had died of malignant brain tumors. Although earlier press reports had been higher, medical specialists at the company were quoted as saying that nine of the brain cancers "were winnowed out of the final statistical findings."

NIOSH was blindsided by Union Carbide's tactics. When the agency released its own findings two weeks later, media attention already had waned. NIOSH had counted 23 brain-tumor deaths, a rate that was double the national average. And it blamed the deaths on chemicals at the plant.

Only one of 23 brain-cancer deaths at Union Carbide's plant in Texas City was included in an industry-sponsored study of workers at vinyl chloride plants.John Everett for the Center for Public Integrity

'It still hurts'

The chemical industry has used its most recent studies in lawsuits to argue that vinyl chloride doesn't cause brain tumors. Frank and Joanne Branham grew up in the small village of McCullom Lake, Illinois, about 60 miles northwest of Chicago, and loved it there. When they got married, they built a home right on the lake. But there was one problem: the odor from a nearby chemical plant.

"There were times when we couldn't have our windows open in the summer," Joanne recalls. "The smell was so bad that it would hurt your eyes." In 1998, they moved to Arizona. Six years later, Franklin Branham started having seizures. Finally, his doctor diagnosed glioblastoma, the same rare brain cancer that had killed Leuvell Malone. Branham had only three months to live. Joanne still breaks down talking about the day Franklin died. "It's been 11 years, but it still hurts," she said.

Not long after her husband's death, Joanne visited McCullom Lake and talked to her former next-door neighbor, Bryan Freund. She discovered that Freund had the same type of cancer. Freund's next-door neighbor, Kurt Weisenberger, had it, too.

Joanne said it was obvious to all of them that the cause was environmental. “It doesn’t take a scientist,” she said. “That just doesn’t happen.” They hired an attorney and filed a lawsuit claiming that a nearby plant had dumped toxic chemicals into a lagoon. They alleged that they were poisoned by vinyl chloride and other volatile chemicals.

Eventually, 33 people around McCullom Lake developed brain tumors. Freund, one of only two brain cancer survivors from the town, has been dealing with his illness for more than a decade and said he is constantly exhausted. One year ago, he had surgery “to remove a whole bunch of my brain. They’ve taken out so much I cannot believe it,” he said. He’s now back on chemotherapy.

The current owner of the plant, Dow Chemical, denies that people in the community were exposed to vinyl chloride, though it settled the case with the brain cancer victims about a year ago. During the litigation, the company hired expert witnesses who cited the Mundt study to prove that the brain tumors couldn’t have been caused by vinyl chloride.

One such expert, Peter Valberg of Gradient Corp., wrote that the families in McCullom Lake were citing early studies linking vinyl chloride to brain cancer but failed to cite more recent reviews. “These in-depth summaries and updates of worker cohorts do not support a causal link between VC exposure and brain cancer,” Valberg wrote.

Aaron Freiwald, the lawyer for the McCullom Lake families, said the scientific consensus today doesn’t account for the fact that workers were excluded from industry brain cancer studies. “We established that even one accounted-for brain cancer would completely shift the data,” Freiwald said. “If there are at least three additional cases, it seems pretty clear that the literature on vinyl chloride and brain cancer as it is has to be rewritten.”

To: Kurt Straif[StraifK@iarc.fr]
Cc: dkrewski@uottawa.ca[dkrewski@uottawa.ca]; Cogliano, Vincent[cogliano.vincent@epa.gov]; **Ex. 6 - Personal Privacy**
From: Robert Baan
Sent: Wed 2/10/2016 11:07:46 AM
Subject: Jane's Table X, detailed (contd.)
Jane's Table X, detailed; comments KS correction RB.docx

Thank you, Kurt, for your quick reply and useful corrections.

I added my responses in the margin (see attachment).

A few additional points: we may consider indicating all the mechanistic upgrades with a footnote; we should perhaps clarify the terms pharynx and oro/naso/hypopharynx; is 'nasal sinus' meant to be the same as 'paranasal sinus(es)'?

Best regards to all,

Robert

From: Kurt Straif
Sent: Wednesday, February 10, 2016 10:55 AM
To: Robert Baan; Daniel Krewski; Cogliano.Vincent@epamail.epa.gov
Cc: **Ex. 6 - Personal Privacy**
Subject: RE: Jane's Table X, detailed

Dear Robert and all,

Attached are my comments.

Thank you,

Kurt

From: Robert Baan
Sent: 10 February 2016 01:22
To: Daniel Krewski <dkrewski@uottawa.ca>; Cogliano.Vincent@epamail.epa.gov
Cc: Kurt Straif <StraifK@iarc.fr>; **Ex. 6 - Personal Privacy**
Subject: Jane's Table X, detailed

Dear all,

Further to Ron's comments about Jane's Table X ('this Table gives numbers of agents and does not say what they are') I have prepared the attached Table for the different sites in the upper aerodigestive system, in which this information is now included. For example, under 'nasopharynx' the numbers 5 (humans) and 1 (rodents) in Jane's Table X are now identified. However, in some cases Jane's numbers do not completely fit with my Table (to be double-checked). Agents with exact concordance are indicated in red. I guess these would represent the 'overlap' in the additional column that Vincent had proposed.

Before I continue, I value your thoughts.

Best wishes,

Robert

Jane's Table X, detailed

		Humans		Animals
		Sufficient	Limited	Sufficient
nasal cavity and paranasal sinuses	70 NNN-NNK	---		nasal cavity (hamster)
	73 Tobacco smoking	nasal cavity, paranasal sinuses		---
	84 BCME	---		nasal cavity (rat)
	91 Formaldehyde	---	paranasal sinuses	nasal cavity (rat)
	93 Isopropanol	nasal cavity		---
	39 Chromium VI	---	nasal sinus	---
	41 Leather dust	nasal sinus	~~nasal sinus~~	---
	42 Nickel compounds	nasal sinus		---
	44 Wood dust	nasal sinus		---
	55 Ra-226	paranasal sinuses		---
	71 Salted fish	---		nasal cavity/paranasal sinuses (rat)
nasopharynx	25 EBV	nasopharynx		---
	44 Wood dust	nasopharynx		---
	71 Salted fish	nasopharynx		nasopharynx (rat)
	73 Tobacco smoking	nasopharynx		---
	91 Formaldehyde	nasopharynx		---
oral cavity	30 HPV 16	oral cavity		---
	30 HPV 18	---	oral cavity	---
	39 Chromium VI	---		oral cavity (rat)
	64 Alcohol drinking	oral cavity		oral cavity (rat)
	65 Areca nut	---		oral cavity (hamster)
	66 Betel quid+tobacco	oral cavity		---
	67 Betel quid–tobacco	oral cavity		---
	69 Ethanol in alcoholica	---		oral cavity (rat)
	73 Tobacco smoking	oral cavity		---
	74 Smokeless tobacco	oral cavity		oral cavity (rat)
	80 Benzene	---		oral cavity (rat)
	105 TCDD	---		oral cavity (rat)

	109 PCBs	---		oral cavity (rat; PCB 126)
pharynx	30 HPV 16	oropharynx		---
	64 Alcohol drinking	pharynx		---
	66 Betel quid+tobacco	pharynx		---
	72 Second-hand smoke	---	pharynx	---
	73 Tobacco smoking	pharynx		---
tongue	39 Chromium VI	---		tongue (rat)
tonsil	30 HPV 16	tonsil		---
salivary gland	51 Radio-iodines	---	salivary gland	---

To: Robert Baan[BaanR@visitors.iarc.fr]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]; Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Ex. 6 - Personal Privacy
From: Kurt Straif
Sent: Wed 2/10/2016 9:55:29 AM
Subject: RE: Jane's Table X, detailed
Jane's Table X detailed_ks.docx

Dear Robert and all,

Attached are my comments.

Thank you,

Kurt

From: Robert Baan
Sent: 10 February 2016 01:22
To: Daniel Krewski <dkrewski@uottawa.ca>; Cogliano.Vincent@epamail.epa.gov
Cc: Kurt Straif <StraifK@iarc.fr>; Ex. 6 - Personal Privacy
Subject: Jane's Table X, detailed

Dear all,

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Before I continue, I value your thoughts.

Best wishes,

Robert

Jane's Table X, detailed

		Humans		Animals
		Sufficient	Limited	Sufficient
nasal cavity and paranasal sinuses	70 NNN	---		nasal cavity (hamster)
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	93 Isopropanol	nasal cavity		---
	39 Chromium VI	---	nasal sinus	---
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	67 Betel quid–tobacco	oral cavity		---
	69 Ethanol in alcoholica	---		oral cavity (rat)
	73 Tobacco smoking	oral cavity		---
	74 Smokeless tobacco	oral cavity		oral cavity (rat)
	80 Benzene	---		oral cavity (rat)
	105 TCDD	---		oral cavity (rat)

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	72 Second-hand smoke	---	pharynx	---
	73 Tobacco smoking	pharynx		---
tongue	39 Chromium VI	---		tongue (rat)
tonsil	30 HPV 16	tonsil		---
salivary gland	51 Radio-iodines	---	salivary gland	---

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Gibbons, Catherine
Sent: Thur 2/4/2016 9:45:07 PM
Subject: RE: Official Invitation: IARC Monographs Vol. 117, Pentachlorophenol and Some Related Compounds, 4-11 October 2016, Lyon, France

Thank you! This will be very stressful to say the least. But I could not pass up the opportunity!

From: Cogliano, Vincent
Sent: Thursday, February 04, 2016 4:04 PM
To: Gibbons, Catherine <Gibbons.Catherine@epa.gov>
Subject: Re: Official Invitation: IARC Monographs Vol. 117, Pentachlorophenol and Some Related Compounds, 4-11 October 2016, Lyon, France

And congratulations!

On Feb 4, 2016, at 15:57, Gibbons, Catherine <Gibbons.Catherine@epa.gov> wrote:

I also need some advice—which hotel should I stay at? ☺

From: IARC Monograph 117 [mailto:Monograph117@iarc.fr]
Sent: Thursday, January 28, 2016 8:35 AM
To: Gibbons, Catherine <Gibbons.Catherine@epa.gov>
Subject: Official Invitation: IARC Monographs Vol. 117, Pentachlorophenol and Some Related Compounds, 4-11 October 2016, Lyon, France

Official Invitation

***IARC Monographs* on the Evaluation of Carcinogenic Risks to Humans**

Volume 117 – 'Pentachlorophenol and Some Related Compounds'

4-11 October 2016

Lyon, France

Dear Dr Gibbons,

Following our prior correspondence by e-mail, we are pleased to officially invite you to participate in the *IARC Monographs* Working Group for volume 117. The Working Group will meet at the International Agency for Research on Cancer (IARC) in Lyon, France, from Tuesday 4 October 2016 9am through Tuesday 11 October 2016 6pm (Saturday included). **Your participation for the full duration of the meeting is required.**

You will receive a writing assignment shortly. Experience has shown that **on-time completion** of writing assignments and pre-meeting peer-reviews are key to the efficiency of the meeting and the ultimate quality of the *Monographs*. Accordingly, **we expect all participants to comply with the following schedule:**

01.07.2016	**Preliminary drafts and references due to IARC**
05.08.2016	**Peer-reviews due to IARC**
05.09.2016	**Revised drafts and references due to IARC**

During the 8-day *Monograph* meeting, you will be expected to take an active part in peer-reviewing and revising all drafts, and discussing and finalizing the evaluations. The entire volume is the joint product of the Working Group and there are no individually authored sections.

Please note that much of the work during the meeting is done electronically, so it is most helpful if you bring a computer. If this is not possible, please let us know.

We thank you for completing IARC's Declaration of Interests, which we will ask you to update at the *Monograph* meeting. As a condition of your participation, description of any pertinent interests will be disclosed at the meeting and in the published Volume 117.

IARC will publish a summary of the meeting in *The Lancet Oncology* on behalf of the Working Group. You will be requested to complete the conflict-of-interest form used by *The Lancet Oncology*, and their editor will disclose conflicting interests alongside IARC's summary of the meeting.

In the spirit of transparency, IARC will post the names of participants on the *Monographs* programme website in advance of the meeting. It is important that there be **no interference from interested parties with the Working Group**, before or during the meeting. Accordingly, we ask you not to discuss the subject matter with anyone with a conflicting interest and to let us know if anyone attempts to lobby you, send you written materials, or make any offer that may be linked to your participation.

The Agency will provide you with a prepaid ticket for your travel by the most direct route (cheapest economy airfare available) through our travel agent. In addition, you will receive a daily allowance (per diem) and travel allowance as follows:

- Per diem: 170 € per night during the authorized travel period (reduced to 50% during overnight flights);

- Travel allowance: 45 € for each arrival and departure to and from Lyon St Exupéry airport and 25 € to and from other airports on the approved official itinerary.

These allowances are intended to cover your hotel expenses, meals, and other incidental expenses including transfers to and from airport. They will be paid to you on the first day of the meeting upon your submission of an expense claim form and complete supporting documents including incoming boarding passes. We kindly ask you to ensure that all hotel bills are paid directly to the hotel prior to the departure. (U.S. Government employees should note that no U.S. Government funds will be used for their expenses and no honorarium will be paid.) Travel and hotel information is attached, including **a hotel and travel form which we kindly request you to return by 17 June 2016 at the latest.**

We look forward to working with you and welcoming you to Lyon.

Yours sincerely,

Kathryn Z. Guyton, PhD

Responsible Officer for the meeting

Kurt Straif, MD, PhD

Head, IARC Monographs Section

International Agency for Research on Cancer/Centre International de Recherche sur le Cancer

150, cours Albert Thomas

F-69372 Lyon Cedex 08

France

Tel: 33-4-72.73.86.54

Fax: 33-4-72.73.83.19

monograph117@iarc.fr

http://monographs.iarc.fr/

Except for insurance coverage provided for accidents and loss of, or damage to, baggage and personal effects during travel, WHO will not be responsible for any loss, accident, damage or injury suffered by an expert, or any person claiming under such expert, arising in or out of his/her participation in this activity. WHO will not be responsible for any claims which are not covered, or which exceed the coverage provided, under WHO's insurance coverage. Experts serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. It is understood that the execution of this work does not create any employer-employee relationship between yourself and the World Health Organization, of which IARC is a part. Furthermore, experts are required to disclose all circumstances that could give rise to a potential conflict of interest as a result of their membership in the expert committee, advisory group or other activity, in accordance with the procedures established by the Director-General for that purpose.

<Hotel and travel form 117.doc>

<Hotel description and directions.doc>

<Travel_info.doc>

<Lyon_map_with_hotels_IARC_metro.pdf>

To: Robert Baan[BaanR@visitors.iarc.fr]; irusyn@cvm.tamu.edu[irusyn@cvm.tamu.edu]; Cogliano, Vincent[cogliano.vincent@epa.gov]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]; martynts@berkeley.edu[martynts@berkeley.edu]
Cc: Ex. 6 - Personal Privacy; Kurt Straif[StraifK@iarc.fr]
From: Caldwell, Jane
Sent: Tue 2/2/2016 10:04:13 PM
Subject: RE: Jane's Table X, heat maps

Dear Robert et al.,

One of the points we did bring up is that the information on individual agents will be retained in the chapter as separate appendices to the chapter. While the Table gives information on the database entries as a whole and it communicates information on sites and organ overlaps, it does not try to tease out that information on a chemical specific level too. The chemical specific information is going to be available in the chapter or in Yann's.

I think it is a matter of what do you want to communicate with what tool here. I think Table X is a good way to tease out where you have sites with overlap between species. I think the Venns can be a good way to take that information and present it in a way for things that we want to highlight and explore as examples of what this means as a whole.

I think that another level of information on what types of Agents make up the overlaps would be best focused on when the Venn diagrams are presented to illustrate points. You will have a spectrum of endpoints that will have a range of responses from not any or many agents cause cancer for these endpoints in either species, to endpoints that tend to have more hits in either species (i.e., lung and liver). You will have a spectrum of overlap between species for those endpoints that do have some positive hits. In some cases the hits occur commonly in humans and rodents for the same chemical and for some they will not.

I think that you want to layer on that part of the information that tells about what types of agents have overlap in what they induce in both species after you have discerned what endpoints have responses by any agent and then what the overlaps are and are not between species. Some endpoints may have a lot of hits, some may or may not have overlap between species. After you have honed in on what you have information for that give some sort of response at the endpoint level, and you have overlap information, then I think the next logical step is to present what chemicals are contributing to the overlaps.

I think the heat map approach of presenting every chemical and then trying to discern what endpoints have any hits, what the overlaps are is very hard to convey with this database in which some much of what will end up in the heat map is lack of data. Rather than provide the

Agent specific layer of information at the front end of the analyses, I think it would be easier to focus the reader enable for us to interpret what the overlaps are after sites and organs have been identified that have positive response and how many have any overlap. The universe of organ sites and overlaps would then be narrowed to what we have positive data on, so we could then try to figure out what agents made up the overlap and perhaps understand more about the database. It would be a way to focus the discussion on what we have data for, rather than presenting the data for every agent and then trying to discern what we have data for out of a sea of white columns.

I could envision developing a separate figure or table perhaps that took the organ systems with at least one overlapping chemical between species and then presenting the identification of those agents that represent the overlap. Do they seem to be a random group of Agents in which you see overlap or is there a theme? Do these Agents with overlap represent agents in which there are more animal studies or more organ sites extensively examined? For the lung, are these mostly agents that are inhaled particles that have similar characteristics? When you have overlap, is it dominated by radiation?

This is my suggested approach.

Jane Caldwell

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: Tuesday, February 02, 2016 4:08 PM
To: Caldwell, Jane <Caldwell.Jane@epa.gov>; irusyn@cvm.tamu.edu; Cogliano, Vincent <cogliano.vincent@epa.gov>; dkrewski@uottawa.ca; martynts@berkeley.edu
Cc: Ex. 6 - Personal Privacy Kurt Straif <StraifK@iarc.fr>
Subject: Jane's Table X, heat maps

Dear all,

This morning I spoke to Ron Melnick, who is a participant in the *IARC Monographs* Working Group meeting that started today, here in Lyon. He agrees with the Table that Jane proposed, with the additional column(s) that Vincent suggested, and the diagrams that Ivan provided. However, the Table in its present form gives numbers of agents, but does not identify the agents themselves, which the heat maps do (or did...)! Since the heat maps have disappeared, Ron would like to see this information retained, along with the Table. During the recent teleconference it was suggested to at least identify the 'overlapping agents' in Ivan's diagrams, but we may consider to also identify the agents outside the overlap. Perhaps we can find a

creative and clear way of presenting this information.

I value your thoughts.

Robert

From: Robert Baan
Sent: Friday, January 29, 2016 2:53 PM
To: caldwell.jane@epa.gov; irusyn@cvm.tamu.edu; Cogliano.Vincent@epamail.epa.gov; Daniel Krewski
Cc: Ex. 6 - Personal Privacy; martynts@berkeley.edu; Kurt Straif; Helene Lorenzen; cphra@uottawa.ca
Subject: Re: conference call on the inclusion/exclusion of heat-maps

Dear all,

Please find attached my summary of yesterday's discussions and decisions during the teleconference.

I value your comments.

Best regards,

Robert

From: Robert Baan
Sent: Thursday, January 28, 2016 6:18 PM
To: caldwell.jane@epa.gov; irusyn@cvm.tamu.edu; Cogliano.Vincent@epamail.epa.gov; Daniel Krewski
Cc: Ex. 6 - Personal Privacy; martynts@berkeley.edu; Kurt Straif; Helene Lorenzen; cphra@uottawa.ca
Subject: conference call on the inclusion/exclusion of heat-maps

Dear colleagues,

Thank you for your valuable contributions and your constructive comments during this morning's/afternoon's conference call.

Jane's proposed Table X and Vincent's proposed additions to that Table appeared a good basis for consensus within this small group, and a sensible alternative to the heat maps.

We will soon inform Ron and Martyn in more detail about what we agreed upon.

Thanks again for your time and input to help this move forward!

Best regards,

Robert

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Mon 1/25/2016 4:27:12 PM
Subject: Re: Bonjour! and question

Bonjour Vincent!

Thanks so much for the information! With this, we will invite Catherine for the v117 meeting. Jason is an excellent suggestion, and his background in inhalation toxicology and mechanisms could be especially valuable for the upcoming evaluation of welding (likely, v118). I also agree with having Samantha in the representative role, perhaps for a future meeting as well (although not in combination with the other two, to give each an independent experience).

I haven't been following the NC vs Ottawa discussion closely- but have heard from Martyn that he distrusts the latter group's analysis. It would be great to find a stopping point for the ongoing work, especially if there isn't consensus.

Fantastic that you'll be here for the IARC@50 conference! Martyn will speak on the 10 key characteristics, I thought his talk at the US EPA workshop was terrific.

I hope you are surviving the aftermath of the blizzard. John was due to return to DC yesterday, but wisely elected to stay another week in France. :-)

Thanks again for the sage advice, Vince! Best to you and everyone there.
Bonne journée,
Kate

From: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Date: Friday 22 January 2016 at 19:50
To: Kate Guyton <guytonk@iarc.fr>
Subject: Re: Bonjour! and question

Bonjour Kate—Yes! By all means invite Catherine. She'll do a great job and will also grow professionally.

When I had been invited to v106, I replied that I couldn't accept when we had perfectly knowledgeable CMs for TCE and perc who would benefit from the experience. (I also advised that DCM might be included, too.) I sent a list with four names: you, Weihsueh, Glinda, and Cheryl. IARC has gone as far as they could with that list (too far in your case).

My new list is Jason Fritz, Catherine, and Samantha. You really need Jason as someone who understands mechanisms, will dig in, has good insights into mechanistic hypotheses, and who is exceedingly respectful and works well with others. Samantha is more limited in her cancer background and publication record, but she's done well in helping others sort out mechanisms of kidney carcinogenesis. I hope someday another good chemical comes along for her. In the meantime, I'm considering her as a Rep to fill

the invitation you usually send me.

So please go ahead with Catherine, with my full blessing. I've never told her about the Catherinettes, and perhaps it'll be better if she learns about them in France.

Did I ever mention that I was CM of a previous pentachlorophenol assessment in the 90s? But I won't go ahead of people on my list, and I'm probably not good for much beyond advisory groups anymore. I expect to come to Lyon at the time of the IARC50 conference in June.

Do you have any insights into the NC vs Ottawa discussion happening on the v100 scientific publication? I'm going to weigh in on Jane's latest message but need to think some more.

Bonne année et bonne santé !

Vince(nt)

On Jan 22, 2016, at 09:09, Kathryn Guyton <GuytonK@iarc.fr> wrote:

Bonjour Vince!!

Greetings from the land of New Year's kisses and galette! Bonne annee et meilleurs voeux!

Quick (hopefully) question for you: in v117, pentachlorophenol (PCP) will be evaluated. I wanted to seek your advice about inviting Catherine Gibbons to participate on the WG. Although relatively junior, she was the co-chemical manager for the US EPA assessment. This broad perspective, along with her knowledge of the 10 key characteristics, will be valuable as will her needed expertise in evaluating the genotoxicity information. The writing assignments should be manageable in size, thus perhaps it is a good opportunity for her to learn the IARC process. With your support, we will be happy to send her a preliminary invitation.

I also note that Leonid K self-nominated for the meeting; however, we already have sufficient coverage for the animal bioassays, with study authors from the US NTP and JBRC and a third pathology expert. I'll write that we hope to afford him the opportunity at a forthcoming meeting.

I understand Snowmaggedon 2 is bearing down on the greater DC area- enjoy your (hopefully) long weekend, and stay warm!
Thanks again,
Bonne journée,
Kate

This message and its attachments are strictly confidential. If you are not the intended recipient of this message, please immediately notify the sender and delete it. Since its integrity cannot be guaranteed, its content cannot involve the sender's responsibility. Any misuse, any disclosure or publication of its content, either whole or partial, is prohibited, exception made of formally approved use.

To: dkrewski@uottawa.ca[dkrewski@uottawa.ca]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Kurt Straif[StraifK@iarc.fr]
From: Robert Baan
Sent: Mon 1/25/2016 7:50:14 AM
Subject: preparation of teleconference

Ron Melnick is now asking for inclusion of the *limited evidence* in humans (sic), but he does not volunteer to write a page about his example, ethylene oxide ...

Chris Portier has never come up with his text about concordance for a number of leukaemogens, taking account of *limited evidence* in animals. I discussed this with him months ago, and Dan also.

And Ron incorrectly reads my 'more strongly supported concordance' as 'stronger concordance' for the 'yellow-to-red' cells in the heat maps.

No further questions, your honour.

I rest my case.

Robert

From: Ron Melnick <**Ex. 6 - Personal Privacy**
Sent: Monday, January 25, 2016 7:17 AM
To: Robert Baan
Cc: caldwell.jane@epa.gov; Daniel Krewski; Cogliano.Vincent@epamail.epa.gov; Kurt Straif
Subject: Re: preparation of teleconference

Dear Robert,
My response (in blue) to your comments is attached.

Ron

On Sun, Jan 24, 2016 at 2:06 PM, Robert Baan <BaanR@visitors.iarc.fr> wrote:

> Dear Jane, dear Ron,
>
> Thank you both for your contribution to the discussion on the heat maps.
>
> My response (in red) to your comments is attached.
>
> Best regards,
>
> Robert

To: Helene Lorenzen[LorenzenH@iarc.fr]
Cc: Martyn Smith[martynts@berkeley.edu]; Cogliano, Vincent[cogliano.vincent@epa.gov]; IRusyn@cvm.tamu.edu[IRusyn@cvm.tamu.edu]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]; Robert Baan[BaanR@visitors.iarc.fr]; CPHRA (cphra@uottawa.ca)[cphra@uottawa.ca]; Kurt Straif[StraifK@iarc.fr]; Caldwell, Jane[Caldwell.Jane@epa.gov]
From: Ron Melnick
Sent: Sat 1/23/2016 10:37:59 PM
Subject: Re: FW: Doodle for conference call on the inclusion/exclusion of heat-maps

Dear colleagues,

Because I will not be available on the date that the conference call was scheduled for discussion on the inclusion or exclusion of heat maps, I am offering some of my thoughts on this issue.

I am concerned that the heat maps give a misleading perspective on site concordance. They give the appearance of being definitive when in fact there are significant uncertainties due to limitations in the human and animal databases and because entries of sites must meet the high bar imposed by IARC criteria for 'sufficient evidence' in animals or humans.

Dan's statement confirms this point: "the tumor site concordance database is incomplete because of the exclusion of limited animal data" and because "not all animal and human tumor sties will have been adequately evaluated."

The finding of site concordance in humans and in more than one animal species reflects the number of species studied and not necessarily the agents with greatest site concordance.

Because the focus of this analysis is site concordance, all agents that lack adequate studies in both animals and humans should be excluded from the heat maps (e.g., 11 biological agents, occupational exposures, all agents with mechanistic upgrades, etc.). The inclusion of these agents in the heat map gives the appearance of poor site concordance between animals and humans, when by design these agents cannot show site concordance.

If heat maps are to be included, I strongly recommend reducing the entries to 4 groups: 1) no species data, 2) human only, 3) animal only, and 4) human and animal; and, I recommend excluding all agents that lack adequate studies in both animals and humans. In addition, the figure legend must clearly identify all limitations in the database that could affect animal-human concordance.

I also believe that if the heat maps are retained, then the agents/tumor sites with limited evidence in humans should be included. One important chemical affected by this addition is ethylene oxide (limited evidence of lymphoma in women and sufficient evidence of lymphomas in rats); in addition, a significant increase of lymphomas in female mice (but not in male mice) adds support to this site concordance.

I look forward to hearing the outcome of these discussions,

Ron

On Tue, Jan 19, 2016 at 1:46 AM, Helene Lorenzen <LorenzenH@iarc.fr> wrote:

> Hi,
>
> The conference call will finally be held as follows:
>
> | | |
> |---|---|
> | Lyon (France) | Thursday, 28 January 2016, 16:00:00 CET UTC+1 hour |
> | Houston (U.S.A. - Texas) hours | Thursday, 28 January 2016, 09:00:00 CST UTC-6 |
> | San Francisco (U.S.A. - California) 8 hours | Thursday, 28 January 2016, 07:00:00 PST UTC- |
> | Washington DC (U.S.A. - District of Columbia) UTC-5 hours | Thursday, 28 January 2016, 10:00:00 EST |
> | Salt Lake City (U.S.A. - Utah) hours | Thursday, 28 January 2016, 08:00:00 MST UTC-7 |
> | Corresponding UTC (GMT) | Thursday, 28 January 2016, 15:00:00 |
>
> Unfortunately, there was no time when you were all available. Sorry Ron, might you be able to make yourself available after all?
>
> **Please also see the attached document prepared by Dan.**

The teleconference will be held via Gotomeeting. Below you will find the log-in information:

Heat-maps discussion

Please join my meeting from your computer, tablet or smartphone.

https://global.gotomeeting.com/join/883143341

You can also dial in using your phone.

Ex. 6 - Personal Privacy

More phone numbers

Ex. 6 - Personal Privacy

With best regards,

Helene

Helene Lorenzen-Augros

Assistant, IARC Monographs Section

International Agency for Research on Cancer/

Centre International de Recherche sur le Cancer

150, Cours Albert Thomas

F-69372 Lyon cedex 08

France

Tel: 33-(0)4-72.73.85.07

Fax: 33-(0)4-72.73.83.19

lorenzenh@iarc.fr

http://monographs.iarc.fr/

To: Cooper, Glinda[Cooper.Glinda@epa.gov]; Gibbons, Catherine[Gibbons.Catherine@epa.gov]
Cc: DeSantis, Joe[DeSantis.Joe@epa.gov]; Soto, Vicki[Soto.Vicki@epa.gov]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Blaine, Susan[Susan.Blaine@icfi.com]
From: EPA_Sys-Review
Sent: Tue 12/15/2015 2:45:11 PM
Subject: FW: Reminder to Send Presentation Slides: Systematic Review Workshop
Smith_EPA_Characteristics_12-2015.pptx

Slides from Martyn Smith.

KATHERINE WORDEN | Research Assistant | ICF International | 703.713.8787 | katherine.worden@icfi.com

From: Martyn Smith [mailto:martynts@berkeley.edu]
Sent: Tuesday, December 15, 2015 12:03 AM
To: EPA_Sys-Review <EPA_Sys-Review@icfi.com>
Cc: Kathryn Guyton <GuytonK@iarc.fr>; Rusyn, Ivan <IRusyn@cvm.tamu.edu>; Gibbons, Catherine <Gibbons.Catherine@epa.gov>
Subject: Re: Reminder to Send Presentation Slides: Systematic Review Workshop

The slides for my presentation are attached.

Thanks, Martyn Smith

From: EPA_Sys-Review <EPA_Sys-Review@icfi.com>
Date: Monday, December 14, 2015 at 12:16 PM
To: EPA_Sys-Review <EPA_Sys-Review@icfi.com>
Subject: Reminder to Send Presentation Slides: Systematic Review Workshop

Dear Presenters,

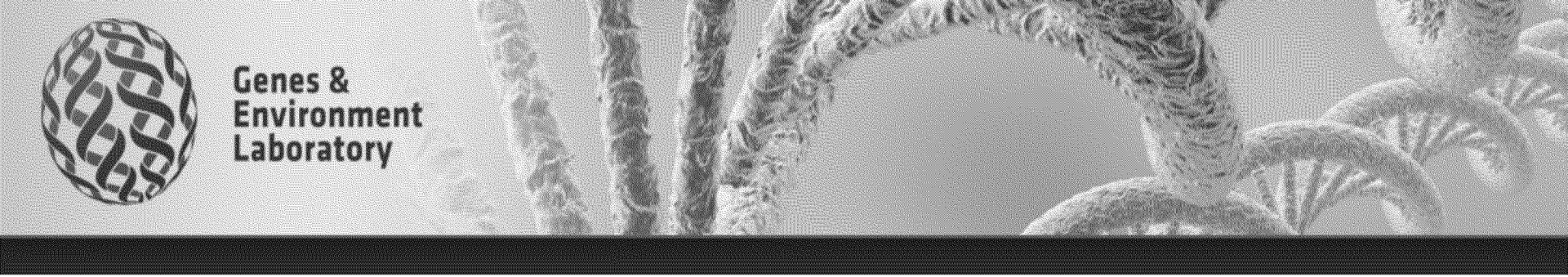
This is a friendly reminder to please send us your presentation slides for EPA's upcoming *Workshop on Advancing Systematic Review for Chemical Risk Assessment* **as soon as possible**.

If you have any questions, please contact Katherine Worden at ICF by phone at 703-713-8787 or email at EPA_Sys-Review@icfi.com.

Thank you!

The Systematic Review Workshop Team

EPA_Sys-Review@icfi.com | 703.713.8787



Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis

Martyn Smith

Director, Superfund Research Program

martynts@berkeley.edu

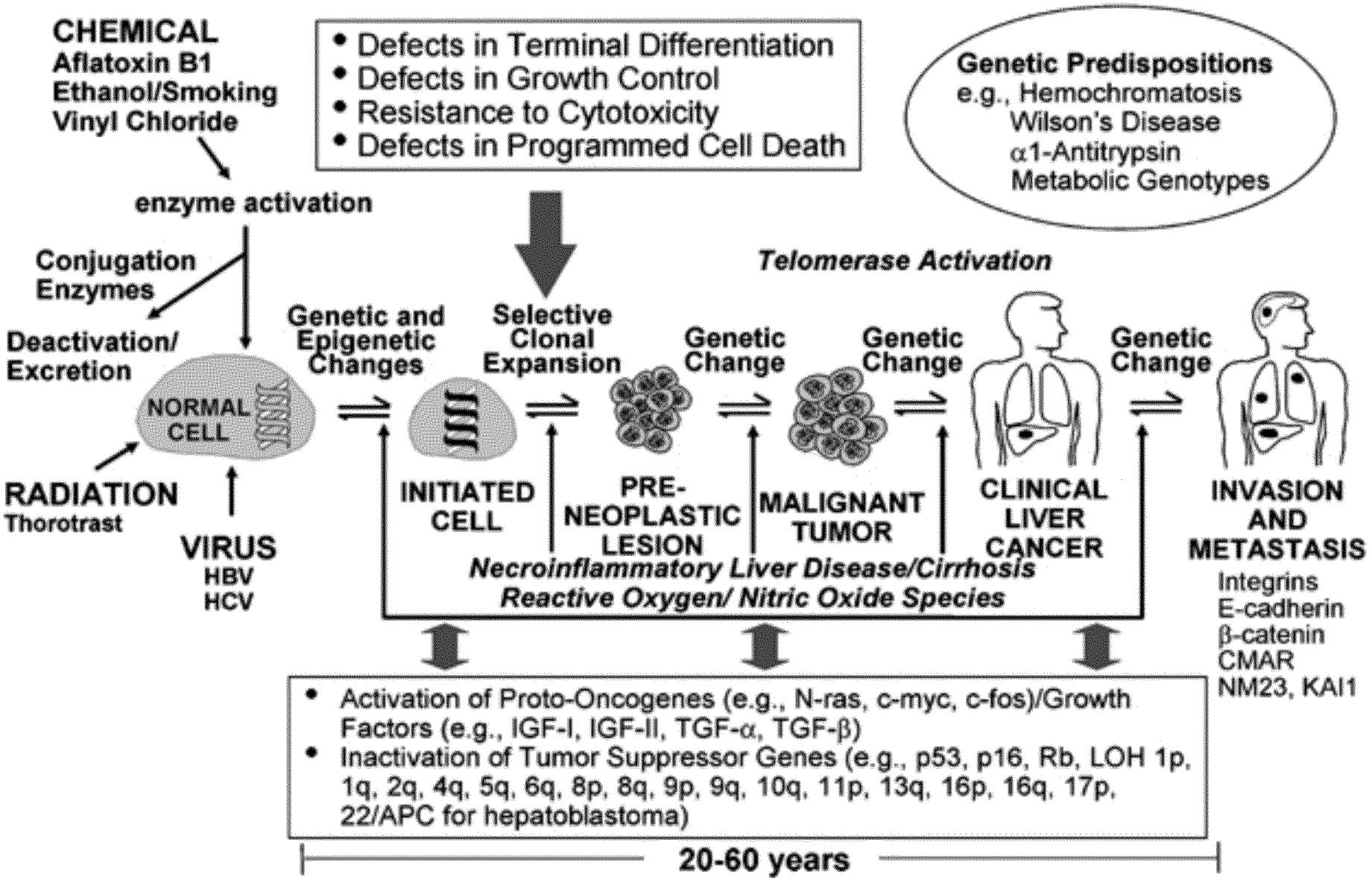
School of Public Health
University of California,
Berkeley

http://superfund.berkeley.edu

Mechanistic data - Problems to address

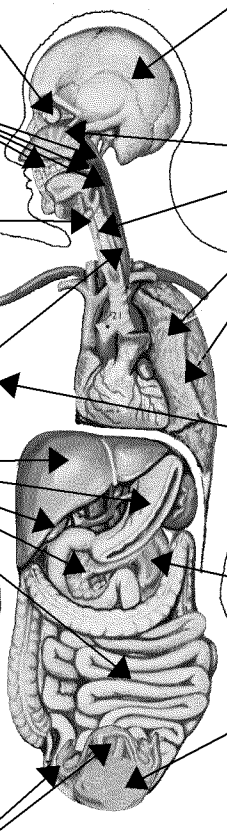
- There is no broadly accepted, systematic method for identifying, organizing, and summarizing mechanistic data for the purpose of decision-making in cancer hazard identification
- Many human carcinogens act via multiple mechanisms causing various biological changes in the multistage process of carcinogenesis – How to capture these diverse effects that lead to cancer and other adverse outcomes for all types of agents?

Human Tumors and Stages of Carcinogenesis



Hussain *et al.,* Oncogene, 2007

IARC Monographs Volume 100: The known causes of human cancer by organ site



Eye
Human immunodeficiency virus type 1
Ultraviolet-emitting tanning devices
Welding

Brain and central nervous system
X-radiation, gamma-radiation

Oral cavity
Alcoholic beverages
Betel quid with tobacco
Betel quid without tobacco
Human papillomavirus type 16
Smokeless tobacco
Tobacco smoking

Pharynx
Alcoholic beverages
Betel quid with tobacco
Human papillomavirus type 16
Tobacco smoking

Nasopharynx
Epstein-Barr virus
Formaldehyde
Salted fish, Chinese-style
Wood dust

Tonsil
Human papillomavirus type 16

Salivary gland
X-radiation, gamma-radiation

Thyroid
Radioiodines, including iodine-131 (exposure during childhood and adolescence)
X-radiation, gamma-radiation

Lung
Aluminium production
Arsenic and inorganic arsenic compounds
Asbestos (all forms)
Beryllium and beryllium compounds
Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)
Cadmium and cadmium compounds
Chromium (VI) compounds
Coal, indoor emissions from household combustion
Coal gasification
Coal-tar pitch
Coke production
Haematite mining (underground)
Iron and steel founding
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
Nickel compounds
Painter (occupational exposure as)
Plutonium
Radon-222 and its decay products
Rubber production industry
Silica dust, crystalline
Soot
Sulfur mustard
Tobacco smoke, secondhand
Tobacco smoking
X-radiation, gamma-radiation

Nasal cavity and paranasal sinus
Isopropyl alcohol manufacture using strong acids
Leather dust
Nickel compounds
Radium-226 and its decay products
Radium-228 and its decay products
Tobacco smoking
Wood dust

Larynx
Acid mists, strong inorganic
Alcoholic beverages
Asbestos (all forms)
Tobacco smoking

Mesothelioma (pleura or peritoneum)
Asbestos (all forms)
Erionite
Painter (occupational exposure as)

Stomach
Helicobacter pylori
Rubber production industry
Tobacco smoking
X-radiation, gamma-radiation

Upper aerodigestive tract
Acetaldehyde associated with consumption of alcoholic beverages

Liver (hepatocytes)
Aflatoxins
Alcoholic beverages
Estrogen-progestogen contraceptives
Hepatitis B virus
Hepatitis C virus
Plutonium
Thorium-232 and its decay products
Tobacco smoking (in smokers and in smokers' children)
Vinyl chloride

Oesophagus
Acetaldehyde associated with consumption of alcoholic beverages
Alcoholic beverages
Betel quid with tobacco
Betel quid without tobacco
Smokeless tobacco
Tobacco smoking
X-radiation, gamma-radiation

Gall bladder
Thorium-232 and its decay products

Biliary tract
Chlonorchis sinensis
Opisthorchis viverrini

Pancreas
Smokeless tobacco
Tobacco smoking

Colon and rectum
Alcoholic beverages
Tobacco smoking
X-radiation, gamma-radiation

Anus
Human immunodeficiency virus type 1
Human papillomavirus type 16

Breast
Alcoholic beverages
Diethylstilbestrol
Estrogen-progestogen contraceptives
Estrogen-progestogen menopausal therapy
X-radiation, gamma-radiation

Urinary bladder
Aluminium production
4-Aminobiphenyl
Arsenic and inorganic arsenic compounds
Auramine production
Benzidine
Chlornaphazine
Cyclophosphamide
Magenta production
2-Naphthylamine
Painter (occupational exposure as)
Rubber production industry
Schistosoma haematobium
Tobacco smoking
ortho-Toluidine
X-radiation, gamma-radiation

Kidney
Tobacco smoking
X-radiation, gamma-radiation

Renal pelvis and ureter
Aristolochic acid, plants containing
Phenacetin
Phenacetin, analgesic mixtures containing
Tobacco smoking

Endometrium
Estrogen menopausal therapy
Estrogen-progestogen menopausal therapy
Tamoxifen

Vagina
Diethylstilbestrol (exposure *in utero*)
Human papillomavirus type 16

Uterine cervix
Diethylstilbestrol (exposure *in utero*)
Estrogen-progestogen contraceptives
Human immunodeficiency virus type 1
Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Tobacco smoking

Vulva
Human papillomavirus type 16

Ovary
Asbestos (all forms)
Estrogen menopausal therapy
Tobacco smoking

Penis
Human papillomavirus type 16

Multiple sites (unspecified)
Cyclosporine
Fission products, including Strontium-90
X-radiation, gamma-radiation (exposure *in utero*)

All cancers combined
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin

Bone
Plutonium
Radium-224 and its decay products
Radium-226 and its decay products
Radium-228 and its decay products
X-radiation, gamma-radiation

Endothelium (Kaposi sarcoma)
Human immunodeficiency virus type 1
Kaposi sarcoma herpes virus

Leukaemia/lymphoma
Azathioprine
Benzene
Busulfan
1,3-Butadiene
Chlorambucil
Cyclophosphamide
Cyclosporine
Epstein-Barr virus
Etoposide with cisplatin and bleomycin
Fission products, including Strontium-90
Formaldehyde
Helicobacter Pylori
Hepatitis C virus
Human immunodeficiency virus type 1
Human T-cell lymphotropic virus type 1
Kaposi sarcoma herpes virus
Melphalan
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
Phosphorus-32, as phosphate
Rubber production industry
Semustine [1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, or methyl-CCNU]
Thiotepa
Thorium-232 and its decay products
Tobacco smoking
Treosulfan
X-radiation, gamma-radiation

Group 1 agents with less than *sufficient* evidence in humans
2,3,4,7,8-Pentachlorodibenzofuran
3,4,5,3',4'-Pentachlorobiphenyl (PCB-126)
4,4'-Methylenebis(2-chloroaniline) (MOCA)
Alpha- and beta-particle emitters
Areca nut
Aristolochic acid
Benzidine, dyes metabolised to
Benzo[*a*]pyrene
Ethanol in alcoholic beverages
Ethylene oxide
Etoposide
Ionizing radiation (all types)
Neutron radiation
N-Nitrosonornicotine (NNN) and 4-(*N*-nitroso-methylamino)-1-(3-pyridyl)-1-butanone (NNK)
Ultraviolet radiation

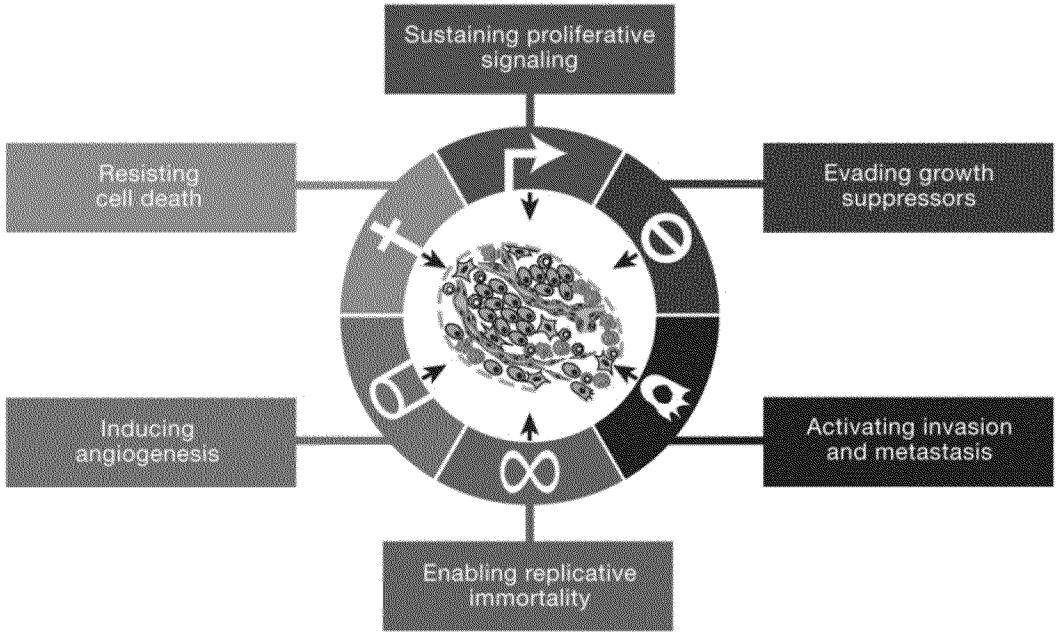
Skin (melanoma)
Solar radiation
Ultraviolet-emitting tanning devices

Skin (other malignant neoplasms)
Arsenic and inorganic arsenic compounds
Azathioprine
Coal-tar distillation
Coal-tar pitch
Cyclosporine
Methoxsalen plus ultraviolet A
Mineral oils, untreated or mildly treated
Shale oils
Solar radiation
Soot
X-radiation, gamma-radiation

Section of the IARC Monographs (IMO)

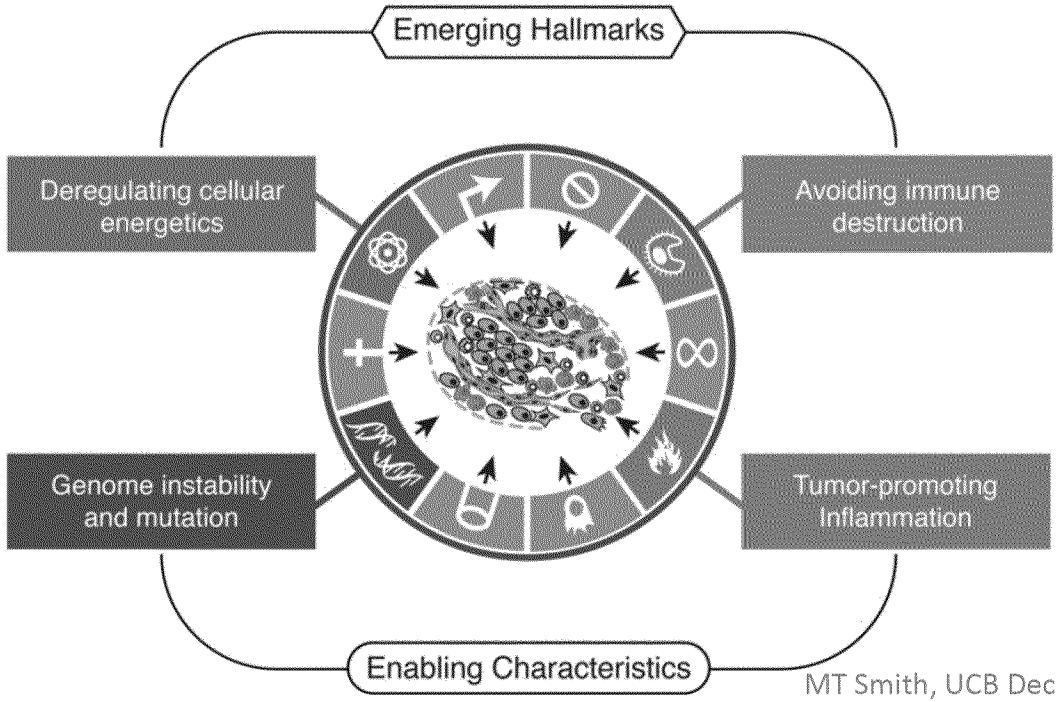
Two meetings held at IARC in 2012 on concordance and mechanisms

EPAHQ_0000560



HALLMARKS OF CANCER

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative immortality
5. Inducing aberrant angiogenesis
6. Activating invasion & metastasis



Emerging Hallmarks

- Reprogramming energy metabolism
- Evading immune destruction

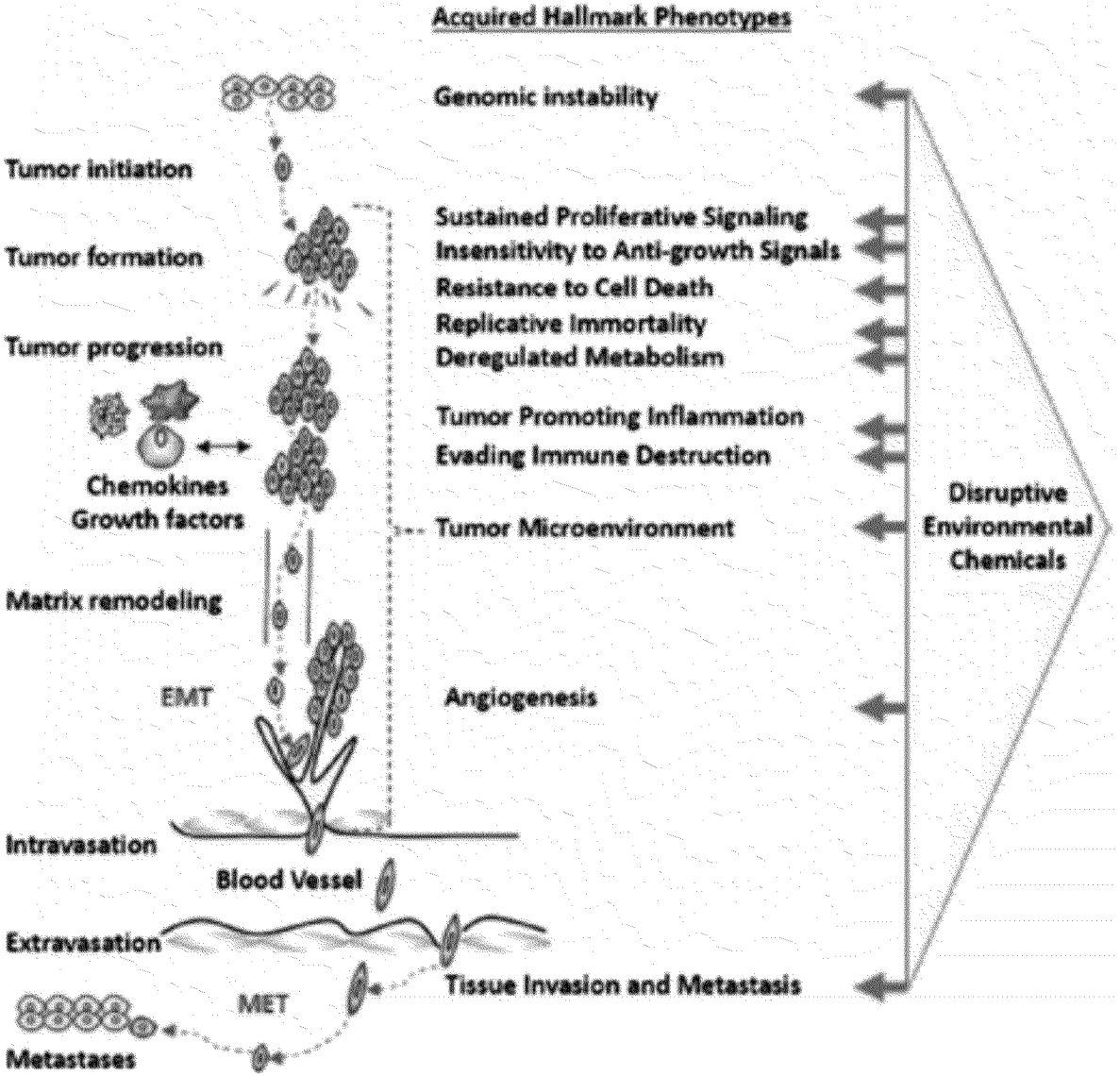
Enabling Characteristics

- Genomic instability and mutation
- Inflammation

MT Smith, UCB Dec 2015

Hanahan and Weinberg 2011

Chemicals and other stressors act at different points on the disease continuum



"Considering the multistep nature of cancer and the acquired capabilities implied by each of these hallmarks, it is therefore a very small step to envision how a series of complementary exposures acting in concert might prove to be far more carcinogenic than predictions related to any single exposure might suggest. Interacting contributors need not act simultaneously or continuously, they might act sequentially..."

Goodson et al. Carcinogenesis. 2015 Jun; 36(Suppl 1): S254–S296.

Review team	Chemical name	Disruptive action on key mechanism/pathway	Low-dose effect (LDE, LLDE, NLDE, threshold, unknown)
Angiogenesis	Diniconazole	Vascular cell adhesion molecule and cytokine signaling	Threshold (H-PC) (36 =TOXCAST)
	Chlorothalonil	Thrombomodulin, vascular proliferation and cytokine signaling	Unknown (H-PC) (36), NLDE (A-*in vivo*) (38 in Amphibians)
Immune system evasion	Pyridaben	Chemokine signaling, TGF-β, FAK, HIF-1a, IL-1a pathways	Unknown (H-CL, H-PC, A-CL) (36,139,140), threshold (A-I) (141)
	Triclosan	Chemokine signaling, TGF-β, FAK, IL-1a pathways	Threshold (H-CL, H-PC, A-I) (36,142–144), LDE (A-I, H-CL) (145,146) None of these papers (142-146) show immune evasion

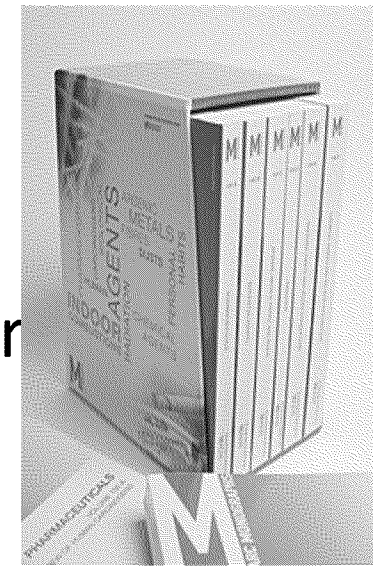
Examples of endpoints used to support conclusions of Goodson et al. --

MT Smith, UCB Dec 2015

Problem is that assay endpoints don't match hallmarks

Dilemma: Cancer or Carcinogens

- Hallmarks are the biological characteristics of cancer cells and tumors in general, NOT the characteristic properties of human carcinogens
- Need to identify the key characteristics of human carcinogens
- IARC Working Group did this in 2012 and subsequently scientists at EPA, IARC and elsewhere determined how these character could be searched for systematically



Multiple Mechanisms of IARC Group 1 Carcinogens

[KZ Guyton….MT Smith, Mut Res 681; 230, 2009]

	Carcinogen			
Mechanisms	AFB1	As+3	Asbestos	Benzene
DNA damage	+	+	-	+
Gene mutation	+	-	+	-
Chrom mutation	+	+	+	+
Aneuploidy	-	+	+	+
Epigenetic	+	+		+
Receptor signaling	-	+	+	
Other signaling	-	+		+
Immune effects	+	+	+	+
Inflammation	+	+	+	+
Cytotoxicity	+	+	+	+
Mitogenic	-	+		-
Gap junction	+	+		+

Key Characteristics of Human Carcinogens

Key characteristic:
1. Is Electrophilic or can be metabolically activated
2. Is Genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces Epigenetic Alterations
5. Induces Oxidative Stress
6. Induces chronic inflammation
7. Is Immunosuppressive
8. Modulates receptor-mediated effects
9. Causes Immortalization
10. Alters cell proliferation, cell death, or nutrient supply

Evidence that these characteristics are observed, especially in humans or as intermediate biomarkers in human specimens can provide biological plausibility for epidemiological findings and/or early warning if no epidemiology exists

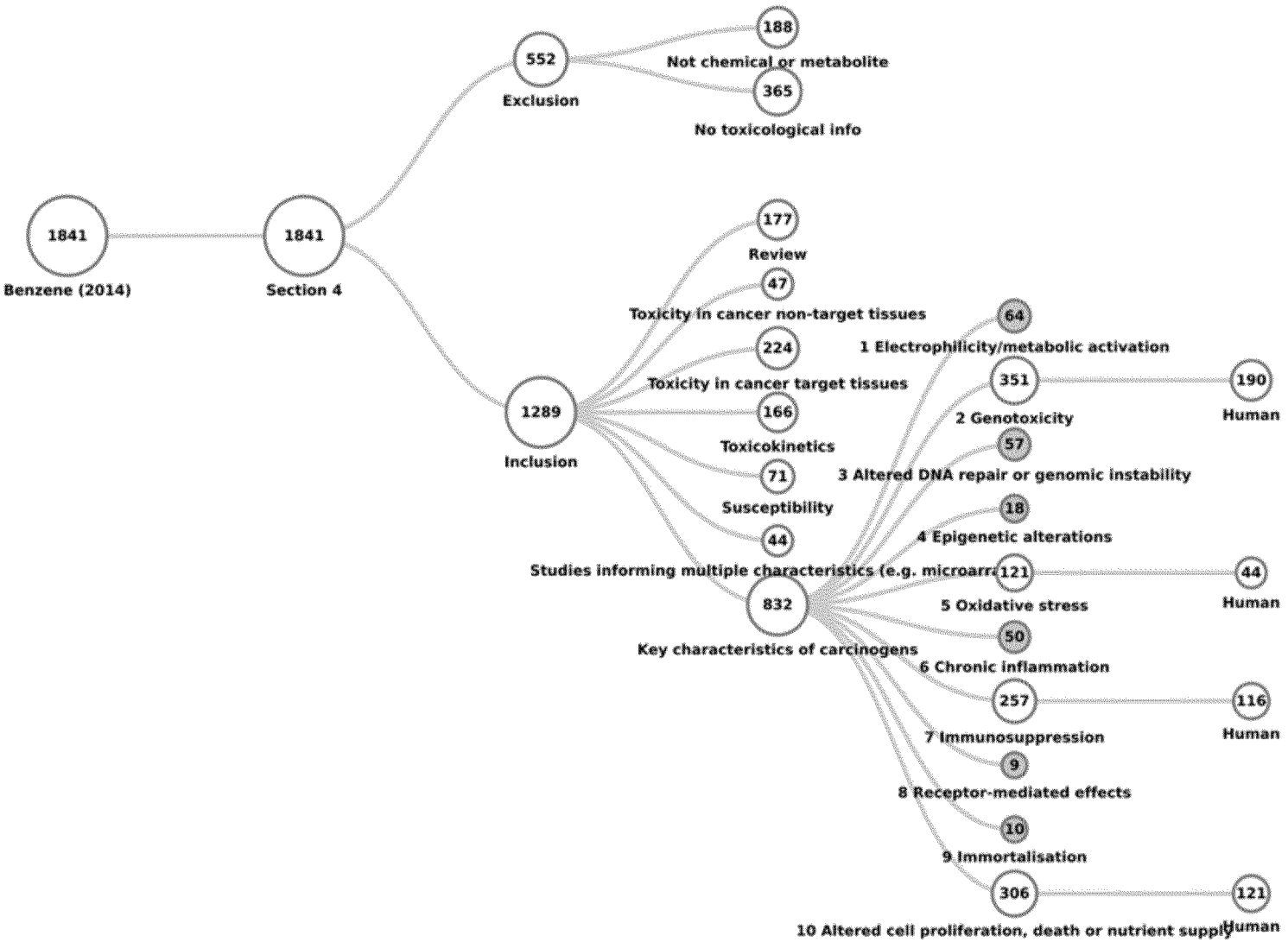
Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert P, Hecht SS, Bucher JR, Stewart BW, Baan R, Cogliano VJ and K Straif. *Env Health Persp.*, *in press*, http://ehp.niehs.nih.gov/15-09912/

Characteristic	Examples of relevant evidence
1. Is Electrophilic or Can Be Metabolically Activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone, etc), formation of DNA and protein adducts.
2. Is Genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei).
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces Epigenetic Alterations	DNA methylation, histone modification, microRNA expression
5. Induces Oxidative Stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)

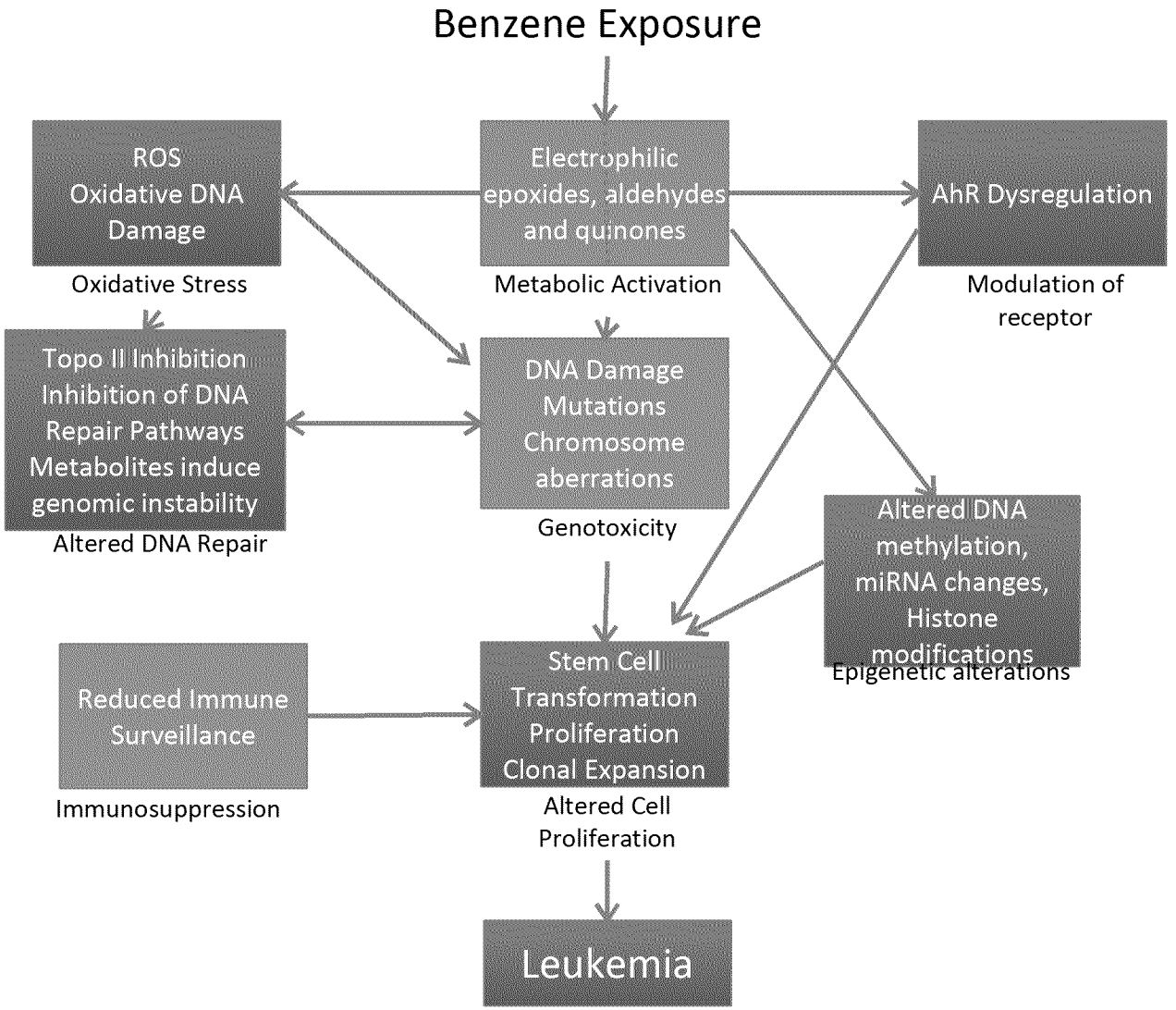
Characteristic	Examples of relevant evidence
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is Immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
9. Causes Immortalization	Inhibition of senescence, cell transformation, altered telomeres
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Benzene Mechanistic Data Search

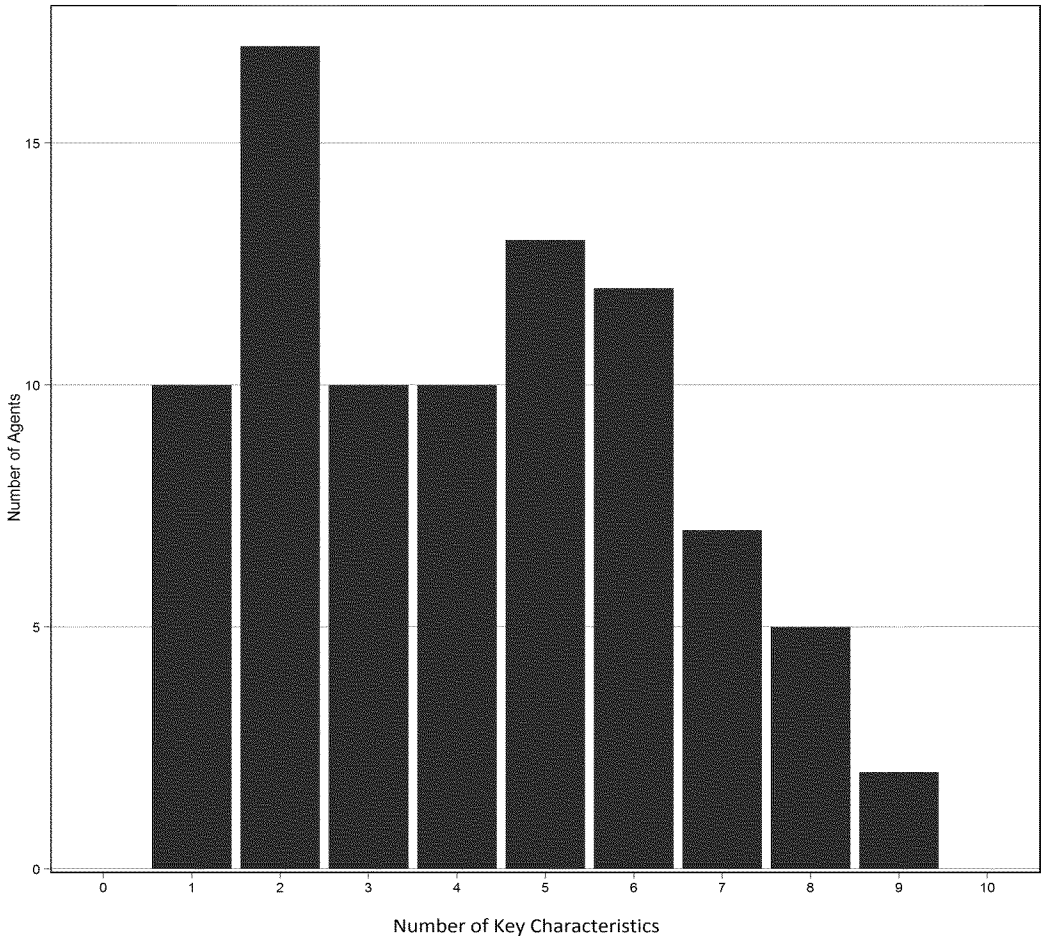
conducted using the Health Assessment Workplace Collaborative (HAWC) Literature Search tool (https://hawcproject.org/)



Benzene Example: An Adverse Outcome Network Involving 8 Key Characteristics



Number of IARC Group-1 Agents Demonstrating Multiple Key Characteristics



D. Krewski et al. in Monograph from IARC Working Group on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', in press.

Implications of 'key characteristics'

- Lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications.
- Shows carcinogens tend to act through multiple mechanisms – separation into genotoxic and non-genotoxic actions of little value
- Allows development of credible Adverse Outcome Networks based on systematic review
- Could be developed for specific cancers and other adverse outcomes
- HT assays need to be developed based on characteristics and hallmarks. Current ones flawed.

An Agency-Academia Collaboration

- **IARC**: Kathryn Z. Guyton, Robert Baan and Kurt Straif
- **US EPA**: Catherine F. Gibbons, Jason M. Fritz, David M. DeMarini, Jane C. Caldwell, Robert Kavlock, Vincent Cogliano
- **NTP**: John R. Bucher
- **Academia**: Ivan Rusyn, Paul Lambert, Stephen S. Hecht, Bernard W. Stewart
- **Thun**: Christopher Portier
- **Other members** of the IARC WG: Lawrence Banks; Frederick A. Beland,; James A. Bond; Maarten C. Bosland; Bice Fubini; Bernard D. Goldstein; Kari Hemminki; Mark A. Hill; Charles Jameson; Agnes B. Kane; Daniel Krewski; Ronald Melnick; Jerry M. Rice; Leslie Stayner; Robert L. Ullrich; Harri Vainio; Paolo Vineis; Michael P. Waalkes; and, Lauren Zeise.
- MTS was supported by NIEHS SRP grant P42ES004705.

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Jarabek, Annie
Sent: Mon 11/30/2015 9:08:32 PM
Subject: RE: Glyphosate letter from 96 scientists

Indeed!

Annie

Annie M. Jarabek

Senior Toxicologist

National Center for Environmental Assessment (NCEA)

Deputy Director

Human Health Risk Assessment (HHRA) research program

US EPA

RTP, NC 27711

Mobile (*Best way to reach me)*: 919.637.6016

Office: 919.541.4847

Email: jarabek.annie@epa.gov

From: Cogliano, Vincent
Sent: Sunday, November 29, 2015 6:03 PM
To: Olden, Kenneth <Olden.Kenneth@epa.gov>; ORD-NCEA-IRIS <ORDNCEAIRIS@usepa.mail.onmicrosoft.com>; ORD-NCEA-IRIS-Extended <ORDNCEAIRISExtended@epa.gov>

Cc: Kurt Straif <straif@iarc.fr>; Kate Guyton <GuytonK@iarc.fr>; Cogliano, Vincent <cogliano.vincent@epa.gov>
Subject: FYI: Glyphosate letter from 96 scientists

Hello everyone--If you're following the glyphosate story, it's about to get more interesting . . .

From: Chris Portier <cportier@me.com>
Date: November 27, 2015 at 7:22:36 AM EST
To: "Dr. Linda Birnbaum" <birnbaumls@niehs.nih.gov>, "John Bucher (NIH/NIEHS)" <bucher@niehs.nih.gov>, Thomas Burke <burke.thomas@epa.gov>, Thomas Sinks <sinks.tom@epa.gov>
Subject: Fwd: EFSA Glyphosate Recommendations

FYI. This went out this morning and is embargoed for public release until 0:00 CET on Monday.

C.

Begin forwarded message:

From: Chris Portier <cportier@me.com>

Date: November 27, 2015 at 10:25:35 AM GMT+1

To: Andreas rummel <ak.rummel@t-online.de>, "Sass, Jennifer" <jsass@nrdc.org>, Angeliki Lysimachou <angeliki@pan-europe.info>, Meg Sears <meg@preventcancernow.ca>, Ann Doherty <amsterdamfarmer@xs4all.nl>, Martin Pigeon <martin@corporateeurope.org>, Stéphane Foucart <foucart@lemonde.fr>, Danny Hakim <hakim@nytimes.com>

Subject: EFSA Glyphosate Recommendations

Dear Addressees,

You have expressed an interest in opinions I or my colleagues might wish to express concerning the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." Attached to this email is an open letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and written a joint criticism of aspects of the EFSA review. Public release of this letter is **EMBARGOED**! Please do not release this letter before 0:00 CET, Monday 30 November, 2015. I will be happy to answer any questions you may have about the content of this letter; my contact information is on the letter. For those of you wishing to prepare newspaper articles or web articles on this letter and/or this issue, I have prepared three quotes from me that you are welcome to use. These are below.

Sincerely,

Prof. Christopher J. Portier

QUOTES:

"My reason for doing all of this work is quite simple, it does the science of risk assessment a disservice when carefully developed methods for analyzing and interpreting the evidence are put aside in favor of ad-hoc approaches that are either wrong, or not amenable to scrutiny by the broader scientific community.

For science to be effective in guiding public health decisions, there needs to be clarity, rigor, transparency, and common sense . The EFSA assessment has serious deficits in all of these areas.

Most importantly, to blindly assess the safety of pure glyphosate to which few people are exposed without considering the evidence on the glyphosate formulations that people are really exposed to is both scientifically flawed and makes little sense to the public."

To: Cogliano, Vincent[cogliano.vincent@epa.gov]; Olden, Kenneth[Olden.Kenneth@epa.gov]; Bussard, David[Bussard.David@epa.gov]; Birchfield, Norman[Birchfield.Norman@epa.gov]; Ross, Mary[Ross.Mary@epa.gov]; Vandenberg, John[Vandenberg.John@epa.gov]
From: Flowers, Lynn
Sent: Mon 11/30/2015 11:52:03 AM
Subject: Re: FYI: Glyphosate letter from 96 scientists

There goes our peer review panel!!

Sent from my iPhone

On Nov 29, 2015, at 6:03 PM, Cogliano, Vincent <cogliano.vincent@epa.gov> wrote:

Hello everyone--If you're following the glyphosate story, it's about to get more interesting . . .

From: Chris Portier <cportier@me.com>
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<EFSA-Glyphosate-Letter.pdf>

To: Martyn Smith[martynts@berkeley.edu]; Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Fritz, Jason[Fritz.Jason@epa.gov]; 'Bernard Stewart'[Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU]; Caldwell, Jane[Caldwell.Jane@epa.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]; 'Paul Lambert'[plambert@wisc.edu]; DeMarini, David[DeMarini.David@epa.gov]; bucher@niehs.nih.gov[bucher@niehs.nih.gov]; 'Chris Portier'[cportier@me.com]; Gibbons, Catherine[Gibbons.Catherine@epa.gov]; lambert@oncology.wisc.edu[lambert@oncology.wisc.edu]; hecht002@umn.edu[hecht002@umn.edu]; 'Robert Baan'[BaanR@iarc.fr]; Kurt Straif[StraifK@iarc.fr]; 'Rusyn, Ivan'[IRusyn@cvm.tamu.edu]
From: Kathryn Guyton
Sent: Wed 11/25/2015 7:15:28 PM
Subject: Re: Online now - EHP 15-09912-REV-Smith

Dear Martyn, Dear all,
Hearty congratulations (and ohe from Brasilia!). See the announcement under Monograph News, http://monographs.iarc.fr
Best,
Kate

From: Martyn Smith <martynts@berkeley.edu>
Date: Tuesday 24 November 2015 at 20:10
To: "'Cogliano, Vincent'" <cogliano.vincent@epa.gov>
Cc: "'Fritz, Jason'" <Fritz.Jason@epa.gov>, 'Bernard Stewart' <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>, "'Caldwell, Jane'" <Caldwell.Jane@epa.gov>, "'Kavlock, Robert'" <Kavlock.Robert@epa.gov>, 'Paul Lambert' <plambert@wisc.edu>, "'DeMarini, David'" <DeMarini.David@epa.gov>, "bucher@niehs.nih.gov" <bucher@niehs.nih.gov>, 'Chris Portier' <cportier@me.com>, "'Gibbons, Catherine'" <Gibbons.Catherine@epa.gov>, Kate Guyton <guytonk@iarc.fr>, "lambert@oncology.wisc.edu" <lambert@oncology.wisc.edu>, "hecht002@umn.edu" <hecht002@umn.edu>, 'Robert Baan' <BaanR@iarc.fr>, Kurt Straif <StraifK@iarc.fr>, "'Rusyn, Ivan'" <IRusyn@cvm.tamu.edu>
Subject: Online now - EHP 15-09912-REV-Smith

Our EHP paper on the key characteristics of carcinogens has just been published on-line. Retweet at #carcinogens http://1.usa.gov/1XcVlpa

Best Martyn

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Fritz, Jason[Fritz.Jason@epa.gov]; 'Bernard Stewart'[Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU]; Caldwell, Jane[Caldwell.Jane@epa.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]; 'Paul Lambert'[plambert@wisc.edu]; DeMarini, David[DeMarini.David@epa.gov]; bucher@niehs.nih.gov[bucher@niehs.nih.gov]; 'Chris Portier'[cportier@me.com]; Gibbons, Catherine[Gibbons.Catherine@epa.gov]; 'Kate Guyton'[GuytonK@iarc.fr]; lambert@oncology.wisc.edu[lambert@oncology.wisc.edu]; hecht002@umn.edu[hecht002@umn.edu]; 'Robert Baan'[BaanR@iarc.fr]; 'Kurt Straif'[straifk@iarc.fr]; 'Rusyn, Ivan'[IRusyn@cvm.tamu.edu]
From: Martyn Smith
Sent: Tue 11/24/2015 10:10:14 PM
Subject: Online now - EHP 15-09912-REV-Smith
Smith et al_ehp.1509912.pdf

Our EHP paper on the key characteristics of carcinogens has just been published on-line. Retweet at #carcinogens http://1.usa.gov/1XcVIpa

Best Martyn

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Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

Martyn T. Smith, Kathryn Z. Guyton, Catherine F. Gibbons, Jason M. Fritz, Christopher J. Portier, Ivan Rusyn, David M. DeMarini, Jane C. Caldwell, Robert J. Kavlock, Paul Lambert, Stephen S. Hecht, John R. Bucher, Bernard W. Stewart, Robert Baan, Vincent J. Cogliano, and Kurt Straif

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Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

Martyn T. Smith[1], Kathryn Z. Guyton[2], Catherine F. Gibbons[3], Jason M. Fritz[3], Christopher J. Portier[4,10], Ivan Rusyn[5], David M. DeMarini[3], Jane C. Caldwell[3], Robert J. Kavlock[3], Paul Lambert[6], Stephen S. Hecht[7], John R. Bucher[8], Bernard W. Stewart[9], Robert Baan[2], Vincent J. Cogliano[3], and Kurt Straif[2]

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Address correspondence to Martyn T. Smith, Division of Environmental Health Sciences, School of Public Health, Li Ka Shing Center, Rm 386, University of California, Berkeley,

Berkeley, California 94720-7356 USA. Telephone: (510) 642-8770. Fax: (510) 642-0427. Assistant: (510) 643-5100. E-mail: martynts@berkeley.edu

Running title: Characteristic properties of human carcinogens

Acknowledgments: We thank all other members of the 2012 Working Group who attended the workshops in Lyon, France for important discussion including: Lawrence Banks, International Centre for Genetic Engineering and Biotechnology, Italy; Frederick A. Beland, National Center for Toxicological Research, USA; James A. Bond, Chemico-Biological Interactions, USA; Maarten C. Bosland, University of Illinois at Chicago, USA; Bice Fubini, University of Torino, Italy; Bernard D. Goldstein, University of Pittsburgh, USA; Kari Hemminki, German Cancer Research Center, Germany; Mark A. Hill, University of Oxford, United Kingdom; Charles William Jameson, CWJ Consulting LLC, USA; Agnes B. Kane, Brown University, USA; Daniel Krewski, University of Ottawa, Canada; Ronald Melnick, Ron Melnick Consulting LLC, USA; Jerry M. Rice, Georgetown University Medical Center, USA; Leslie Stayner, University of Illinois at Chicago, USA;; Robert L. Ullrich, University of Texas, USA; Harri Vainio, Finnish Institute of Occupational Health, Finland; Paolo Vineis, Imperial College London, United Kingdom; Michael P. Waalkes, National Institute of Environmental Health Sciences, USA; and, Lauren Zeise, California Environmental Protection Agency, USA. MTS was supported by NIEHS grant P42ES004705.

Disclaimers: This paper does not necessary reflect the views and policies of the U.S. Environmental Protection Agency. Mention of trade names does not constitute endorsement or recommendation for use.

Competing financial interests: MTS has received consulting fees from attorneys representing plaintiffs and defense in cases involving exposure to benzene and other chemical agents. The other authors have no conflicts of interest to report.

Abstract

Background: A recent review by the International Agency for Research on Cancer (IARC) updated the assessments of the more than 100 agents classified as Group 1, carcinogenic to humans (IARC Monographs Volume 100, parts A-F). This exercise was complicated by the absence of a broadly accepted, systematic method for evaluating mechanistic data to support conclusions regarding human hazard from exposure to carcinogens.

Objectives and Methods: IARC therefore convened two workshops in which an international Working Group of experts identified 10 key characteristics, one or more of which are commonly exhibited by established human carcinogens.

Discussion: These characteristics provide the basis for an objective approach to identifying and organizing results from pertinent mechanistic studies. The ten characteristics are the abilities of an agent to: (1) act as an electrophile either directly or after metabolic activation; (2) be genotoxic; (3) alter DNA repair or cause genomic instability; (4) induce epigenetic alterations; (5) induce oxidative stress; (6) induce chronic inflammation; (7) be immunosuppressive; (8) modulate receptor-mediated effects; (9) cause immortalization; and (10) alter cell proliferation, cell death, or nutrient supply.

Conclusion: We describe the use of the 10 key characteristics to conduct a systematic literature search focused on relevant endpoints and construct a graphical representation of the identified mechanistic information. Next, we use benzene and polychlorinated biphenyls as examples to illustrate how this approach may work in practice. The approach described is similar in many respects to those currently being implemented by the U.S. EPA□s IRIS Program and the U.S. National Toxicology Program.

Introduction

Recently, the International Agency for Research on Cancer (IARC) completed a review of all its Group 1 human carcinogens and updated information on tumor sites and mechanisms of carcinogenesis (IARC Monograph Volume 100A-F). About half of the agents classified in Group 1 had been last reviewed more than 25 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent studies have demonstrated that many cancer hazards reported in earlier studies were later observed to also cause cancer in other organs or through different exposure scenarios (Cogliano et al. 2011).

In compiling and updating the information for Volume 100A-F, two overarching issues became apparent. First, no broadly accepted systematic method for identifying, organizing, and summarizing mechanistic data for the purpose of decision-making in cancer hazard identification was readily available. Second, the agents documented and listed as human carcinogens showed a number of characteristics that are shared among many carcinogenic agents. Many human carcinogens act via multiple mechanisms causing various biological changes in the multistage process of carcinogenesis. Indeed, cancer was once described by reference to causative agents, with multistage development of tumors being characterized through the impact of particular chemicals described as initiators and promoters of cancer. Subsequently, multistage development of cancer was identified with morphological change being correlated with genetic alterations. The more recent description by Hanahan and Weinberg of hallmarks of cancer is not predicated on morphology or the impact of carcinogens, but on changes in gene expression and cell signaling (Hanahan and Weinberg 2011). These hallmarks are the properties of cancer cells and neoplasms, and are not characteristic of the agents that cause cancer. Tumors attributable to

chemical carcinogens may be distinct by mutational analysis (Westcott et al, 2015), but all neoplasms exhibit the hallmarks. A recent computational toxicology study has shown that chemicals that alter the targets or pathways among the hallmarks of cancer are likely to be carcinogenic (Kleinstreuer et al. 2013). In addition, a series of reviews in *Carcinogenesis* by members of the Halifax Project Task Force utilized the hallmarks framework to identify the carcinogenic potential of low doses and mixtures of chemicals (Harris 2015).

In 2012, participants at two workshops convened by the IARC in Lyon, France extensively debated the mechanisms by which agents identified as human carcinogens (Group 1) produce cancer. The participants concluded that these carcinogens frequently exhibit one or more of 10 key characteristics (Table 1). Herein we describe these 10 key characteristics and discuss their importance in carcinogenesis. These characteristics are properties that human carcinogens commonly show and can encompass many different types of mechanistic endpoints. They are not mechanisms in and of themselves nor are they adverse outcome pathways.

Further, we describe how the 10 key characteristics can provide a basis for systematically identifying, organizing, and summarizing mechanistic information as part of the carcinogen evaluation process. The U.S. Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) in the U.S., as well as the IARC internationally, have recognized a need for such an approach (Rooney et al. 2014). The U.S. National Research Council emphasized the need for consistent, transparent, systematic approaches for the identification, evaluation, and integration of data in EPA's IRIS assessments of carcinogens and elsewhere in human health hazard assessments (NRC 2014).

Progress in the systematic evaluation of published evidence on the adverse health effects of environmental agents has been made through application of methods developed by evidence-based medicine (Koustas et al. 2014). However, mechanistic study databases present a challenge to systematic reviews in that the studies are typically both numerous and diverse, reporting on a multitude of endpoints and toxicity pathways. One recent example of a systematic approach searched for studies on endpoints relevant to nine cancer-related mechanistic categories in identifying and presenting mechanistic evidence on di(2-ethylhexyl)phthalate, a chemical with a complex database of over 3000 research papers (Kushman et al. 2013). In this publication, the categories of mechanistic evidence were identified from a compendium of published reviews. This approach may be difficult to translate to agents with controversial or limited mechanistic evidence. It also would not permit comparisons across agents, including attempts to understand similarities or differences with human carcinogens. Further, it may be biased against the most recent mechanistic and molecular epidemiology studies that have not been the subject of a prior expert review.

To facilitate a systematic and uniform approach to organizing mechanistic data relevant to carcinogens, we propose the use of 10 key characteristics of human carcinogens as a basis for identifying and categorizing scientific findings relevant to cancer mechanisms when assessing whether an agent is a potential human carcinogen. A significant advantage of this approach is that it would encompass a wide range of endpoints of known relevance to carcinogenesis as identified through examination of the IARC Monographs on Group 1 carcinogens. Mechanistic topics can be included regardless of whether they have been the subject of prior expert reviews of any particular chemical. This should introduce objectivity that could reduce reliance on expert opinion, as well as facilitate comparisons across agents. Moreover, at its essence, the approach

may afford a broad consideration of the mechanistic evidence rather than focusing narrowly on independent mechanistic hypotheses or pathways in isolation.

Herein, we demonstrate the applicability of this proposed systematic strategy for searching and organizing the literature using benzene and polychlorinated biphenyls (PCBs) as examples. The mechanistic study database for both of these chemicals is large, comprising over 1,800 studies for benzene and almost 3,900 for PCBs, many with multiple mechanistic endpoints. We conducted systematic literature searches for endpoints pertinent to the 10 key characteristics of human carcinogens, utilizing literature trees to indicate the human and experimental animal studies that reported endpoints relevant to each characteristic. To further indicate their potential contribution to benzene and PCB carcinogenesis, we organized the characteristics into a graphical network representative of an overall mechanistic pathway.

Two recent IARC Monographs (Guyton et al. 2015; Loomis et al. 2015) have applied the 10 key characteristics described here for a variety of agents and also organized the results into graphical networks. Overall, this categorization facilitated objective consideration of the relevant mechanistic information, thereby advancing analyses of hypothesized mechanisms and toxicity pathways. Because mechanistic data may provide evidence of carcinogenicity, and can play a role in up- or downgrading an evaluation based on cancer findings in animals, we suggest that this systematic approach to organizing the available data will assist future IARC Working Groups and other agencies in evaluating agents as potential human carcinogens especially in the absence of convincing epidemiological data on cancer in humans.

Description of the Key Characteristics of Carcinogens

The number of ways by which agents contribute to carcinogenesis can be extensive if all biochemical or molecular endpoints are considered. However, these mechanisms can be grouped into a limited number of categories (e.g., genotoxicity, immunosuppression, etc.). Guyton and coworkers described 15 types of "key events" associated with human carcinogens that collectively represented many carcinogenic mechanisms (Guyton et al. 2009). The experts present at the first of the IARC meetings in 2012 originally identified 24 mechanistic endpoints with several subcategories in each. This number of endpoints was considered too impractical as a guide for categorizing the literature, and the Working Group merged these categories into 10 at the second meeting in 2012, concluding that human carcinogens commonly show one or more of the 10 key characteristic properties listed in Table 1. These represent the majority of established properties of human carcinogens as described below.

Characteristic 1: Is Electrophilic or Can Be Metabolically Activated to Electrophiles

Electrophiles are electron-seeking molecules that commonly form addition products, commonly referred to as adducts, with cellular macromolecules including DNA, RNA, lipids and proteins. Some chemical carcinogens are direct-acting electrophiles, whereas others require chemical conversion within the body (Salnikow and Zhitkovich 2008), or biotransformation by enzymes in a process termed metabolic activation (Miller 1970). Examples of direct-acting electrophilic carcinogens include sulfur mustards and ethylene oxide (Batal et al. 2014; Grosse et al. 2007; IARC 2008; Rusyn et al. 2005). The classic examples of chemical agents that require metabolic activation to become carcinogenic include polycyclic aromatic hydrocarbons, aromatic amines, *N*-nitrosamines, aflatoxins and benzene, which by themselves are relatively inert (Slaga et al.

1980; Smith 1996). A number of enzymes, including cytochrome P450s, flavin mono-oxygenase, prostaglandin synthase and various peroxidases, can biotransform relatively inert chemical compounds to potent toxic and carcinogenic metabolites or reactive intermediates (Hecht 2012; O'Brien 2000). The ability to form adducts on nucleic acids and proteins is a common property of these inherently electrophilic and/or metabolically activated human carcinogens (Ehrenberg 1984).

Characteristic 2: Is Genotoxic

The term genotoxic (Ehrenberg 1973) refers to an agent that induces DNA damage, mutation, or both. DNA damage can be spontaneous in origin through errors of nucleic acid metabolism or can be induced by endogenous or exogenous agents. In some cases the exogenous agents may also be generated endogenously, such as formaldehyde and acetaldehyde, producing a background level of DNA damage. Examples of DNA damage include DNA adducts (a molecule bound covalently to DNA), DNA strand breaks (breaks in the phosphodiester bonds), DNA crosslinks, and DNA alkylation. DNA damage by itself is not a mutation and generally does not alter the linear sequence of nucleotides (or bases) in the DNA, whereas a mutation is a change in the DNA sequence and usually arises as the cell attempts to repair the DNA damage (Shaughnessy 2009).

Mutations can be classified into three groups based on their location or involvement in the genome. Gene or point mutations are changes in nucleotide sequence within a gene (e.g., base substitutions, frameshifts, and small deletions/duplications). Chromosomal mutations are changes in nucleotide sequence that extend over multiple genes (e.g., chromosome aberrations, translocations, large deletions, duplications, insertions, inversions, or micronuclei due to

chromosome breakage). Genomic mutations involve the duplication or deletion of nucleotide sequences of an entire chromosome, an example of which is aneuploidy or formation of micronuclei that contain a centromere. A large proportion of Group 1 carcinogens are genotoxic, as documented in IARC Monographs Volume 100 A-F (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php).

Characteristic 3: Alters DNA Repair or Causes Genomic Instability

Normal cells avoid deleterious mutations by replicating their genomes with high accuracy. However, the fidelity of DNA replication can vary widely depending on the DNA polymerase involved, introducing the possibility of error. Indeed, most spontaneous mutations are caused by polymerase error (Preston et al. 2010). The nature of the error, the flanking sequence, the presence of DNA damage and the ability to correct errors, all impact on the outcome of this process (Arana and Kunkel 2010). As a consequence, defects in processes that determine DNA-replication fidelity can confer strong mutator phenotypes that result in genomic instability. Thus, carcinogens may act not only by producing DNA damage directly, but also by altering the processes that control normal DNA replication or repair of DNA damage. Examples include the inhibition of DNA repair by cadmium (Candeias et al. 2010) and formaldehyde (Luch et al. 2014).

Genomic instability is a well-recognized feature of many cancers (Bielas et al. 2006) and considered to be one of the enabling characteristics of cancer (Hanahan and Weinberg 2011). Cells exposed to ionizing radiation have genetic instability that is a relatively late-occurring event that appears several cell generations after irradiation and results in a reduced ability to

replicate the genotype faithfully (Kadhim et al. 2013). The events indicating genomic instability include chromosome aberrations, gene mutations, microsatellite instability, and apoptosis. These events are observed after exposure to arsenic (Bhattacharjee et al. 2013) and cadmium (Filipic 2012).

Characteristic 4: Induces Epigenetic Alterations

The term "epigenetic" refers to stable changes in gene expression and chromatin organization that are not caused by changes in the DNA sequence itself and can be inherited over cell divisions (Herceg et al. 2013). Epigenetic phenomena, including changes to the DNA methylome and chromatin compaction states, along with histone modification can impact the carcinogenic process by affecting gene expression and DNA repair dynamics (Herceg et al. 2013). A wide range of carcinogens have been shown to deregulate the epigenome, and it has been suggested that their mechanism may involve disruption of epigenetic mechanisms (Pogribny and Rusyn 2013). However, evidence for a causal role of epigenetic changes in cancer caused by Group 1 agents was considered to be limited in Volume 100, and for many agents, their impact on the epigenome was considered to be a secondary mechanism of carcinogenesis (Herceg et al. 2013). Herceg and others (Herceg et al. 2013) have described a wealth of studies demonstrating the impact of carcinogens on epigenetic mechanisms. They note, however, that most carcinogens (even those reviewed for Volume 100 in 2008 and 2009) were evaluated by IARC Working Groups before new data on their epigenetic effects became available. This evolving area will generate new mechanistic data in the years to come.

Characteristic 5: Induces Oxidative stress

Many carcinogens are capable of influencing redox balance within target cells. If an imbalance occurs, favoring formation of reactive oxygen and/or nitrogen species at the expense of their detoxification, this is referred to as oxidative stress. Reactive oxygen species and other free radicals arising from tissue inflammation, xenobiotic metabolism, interruption of mitochondrial oxidative phosphorylation (Figueira et al. 2013), or reduced turnover of oxidized cellular components may play key roles in many of the processes necessary for the conversion of normal cells to cancer cells. However, oxidative stress is not unique to cancer induction and is associated with a number of chronic diseases and pathological conditions, e.g., cardiovascular disease (Kayama et al. 2015), neurodegenerative disease (Chen et al. 2015), and chronic inflammation (Suman et al. 2015). Oxidative stress is also a common occurrence in neoplastic tissue and can be part of the tumor environment (Suman et al. 2015).

Oxidative damage is considered a major factor in the generation of mutations in DNA and over 100 different types of oxidative DNA damage have been identified (Klaunig et al. 2011). At least 24 base modifications are produced by reactive oxygen species, as well as DNA-protein crosslinks and other lesions (Berquist and Wilson 2012), all potentially leading to genomic instability. Oxidative damage to DNA can lead to point mutations, deletions, insertions, or chromosomal translocations, which may cause oncogene activation and tumor suppressor gene inactivation, and potentially initiate or promote carcinogenesis (Berquist and Wilson 2012; Klaunig et al. 2011). Thus, the induction of oxygen radical-induced cellular injury is a characteristic of a set of diverse carcinogens, including radiation, asbestos, and carcinogenic infectious agents.

Characteristic 6: Induces Chronic Inflammation

Chronic inflammation from persistent infections, such as that caused by *H. pylori*, as well as that produced by chemical agents including silica or asbestos fibers, has been associated with several forms of cancer (Grivennikov et al. 2010). Indeed, inflammation has been hypothesized to contribute to multiple aspects of cancer development and progression (Trinchieri 2012) and is an enabling hallmark of cancer (Hanahan and Weinberg 2011). Inflammation acts by both intrinsic and extrinsic pathways. Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signaling, leading to the recruitment and activation of inflammatory cells. These constitute extrinsic pathways linking inflammation to cancer (Multhoff and Radons 2012). On the other hand, intrinsic pathways driven by activation of proto-oncogenes in pre-neoplastic and neoplastic cells recruit host-derived inflammatory cells that accelerate tumor promotion and progression (Grivennikov et al. 2010). Because strong links exist between inflammation and the induction of oxidative stress and genomic instability, it may be difficult to separate out the importance of each of these mechanisms.

Characteristic 7: Is Immunosuppressive

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumor cells. Persistent immunosuppression presents a risk of cancer, especially excess risk for lymphoma. For example, immunosuppression poses a significant risk when it is accompanied by continuing exposure to foreign antigens, such as in people with organ transplants, or when it occurs in individuals who are latently infected with a carcinogenic virus (Hartge and Smith 2007; Smith et al. 2004). Immune suppression differs from other mechanisms of carcinogenesis in that agents that cause immunosuppression may not

directly transform normal cells into potential tumor cells. Potentially neoplastic cells that arise naturally, or that have been transformed by other carcinogens acting by a mechanism such as genotoxicity or by the various mechanisms of action associated with carcinogenic viruses, escape immune surveillance in immunosuppressed individuals. As a result, survival of these cells and their replication to form tumors is greatly facilitated by immune suppression. Several carcinogens act entirely or largely by immunosuppression, often in concert with other Group 1 agents, especially oncogenic infectious agents. The Group 1 agents that act by immunosuppression include Human Immunodeficiency Virus (HIV-1) and the immunosuppressive drug cyclosporin (Rafferty et al. 2012).

Characteristic 8: Modulates Receptor-mediated effects

Numerous carcinogens act as ligands to receptor proteins, including menopausal hormone therapy, 2,3,7,8-tetrachlorodibenzo-para-dioxin and PCBs (Wallace and Redinbo 2013). Receptor-mediated activation broadly falls into two categories: (a) intracellular activation, mediated by nuclear receptors that translocate into the nucleus and act on DNA as transcription factors (Aranda and Pascual 2001); and (b) activation of cell surface receptors that induce signal-transduction pathways resulting in biological responses that involve a variety of protein kinases (Griner and Kazanietz 2007). Most exogenous agents act as agonists by competing for binding with an endogenous ligand; however, there are also receptors for which few or no endogenous ligands have been identified, such as the aryl-hydrocarbon (Ah) receptor (Baek and Kim 2014; Ma 2011). Receptor-mediated activation most often results in changes in gene transcription. Molecular pathways that are regulated through ligand-receptor interaction and are most relevant to carcinogenesis include cell proliferation (e.g., stimulation of the normal proliferative pathways

as is the case for estrogen-dependent tissues and hormone therapy), xenobiotic metabolism, apoptosis, as well as modulation of the bioavailability of endogenous ligands by affecting biosynthesis, bioactivation, and degradation (Rushmore and Kong 2002).

Characteristic 9: Causes Immortalization

Several human DNA and RNA viruses, including various human papillomaviruses, Epstein-Barr virus, Kaposi's sarcoma-associated herpesvirus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, are carcinogenic to humans (Bouvard et al. 2009).
These viruses have evolved multiple molecular mechanisms to disrupt specific cellular pathways to facilitate aberrant replication. Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth (Saha et al. 2010). Recent studies show that virus and host interactions also occur at the epigenetic level (Allday 2013). The result of these viral effects is to immortalize the target tissue cells such that they are not subject to the Hayflick limit, the point at which cells can no longer divide due to DNA damage or shortened telomeres (Klingelhutz 1999). For example, the Human Papillomavirus type-16 (HPV-16) *E6* and *E7* oncogenes are selectively retained and expressed in cervical carcinomas, and expression of *E6* and *E7* is sufficient to immortalize human cervical epithelial cells (Yugawa and Kiyono 2009).

Characteristic 10: Alters Cell Proliferation, Cell Death or Nutrient Supply

There are at least three scenarios related to carcinogenesis in which alterations in cellular replication and/or cell-cycle control have been described. One invokes the predisposition for

unrepaired DNA damage leading to cancer-initiating mutations in replicating cells, another has attempted to identify sustained replication as a key mechanistic event, and a third describes the ability of a transformed cell to escape normal cell-cycle control and to continue replication. A component common to all three scenarios is the evasion of apoptosis or other terminal programming, including autophagy, in at least a proportion of the cell population (Ryter et al. 2014).

Necrotic cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, recruiting inflammatory immune cells to the site of trauma, which can enhance cancer-cell proliferation and promote cancer metastasis (Coussens and Pollard 2011; Coussens et al. 2013; Pollard 2008). In contrast, various forms of apoptosis and autophagy (Galluzzi et al. 2015) have the opposite effect by removing potentially cancerous cells from a population before they acquire the changes permitting malignancy. Many agents affect necrosis, apoptosis and/or autophagy and can have profoundly divergent effects on cancer induction in different tissues.

In addition to cell death caused directly by agent toxicity, cells may die within a tumor as a result of an impaired nutrient supply. Neoplastic cell numbers can increase exponentially, quickly outstripping the supply capabilities of the existing tissue vasculature. Neoangiogenesis, in which new blood vessels grow into a tumor, is key to providing this supply of nutrients. Thus, agents that promote or inhibit angiogenesis will promote or delay tumor growth (Hu et al. 2015).

Cancer cells also usually show quite different cellular energetics, relying on glycolysis for energy even under aerobic conditions (Rajendran et al. 2004). Although a likely consequence of mutation and altered gene expression rather than a cancer-inducing mechanism, any modification

of cellular energetics may reflect an important cancer-relevant switch in the cell or tissue's metabolic state.

Using the key characteristics to systematically identify, organize, and summarize mechanistic information

Step 1: Identifying the relevant information

The starting point for systematic evaluation is to conduct comprehensive searches of the peer-reviewed literature aimed at identifying mechanistic data (Kushman et al. 2013). The searches can be constructed to address a series of study questions in the PECO (population, exposure, comparator, and outcomes) framework (Higgins and Green 2011) wherein endpoints associated with the key characteristics are identified. Specifically, the questions to be answered by the searches are, "Does exposure to the agent induce endpoints associated with one or more specific key characteristic properties of carcinogens"? The population (humans and any relevant experimental systems), exposure (the agent and relevant metabolites) and comparator (the unexposed comparison group or condition) should be sufficiently broad to identify a range of available mechanistic data informative of the overall evaluation of carcinogenic hazard. This approach thus entails comprehensive, targeted literature searches using appropriate Medical Search Heading (MeSH) terms and key words to identify evidence on the 10 key characteristics for the agent(s) or exposure(s) under evaluation.

Additional complementary literature searches may incorporate terms for the agent and its metabolites, alone or in combination with broad terms for carcinogenicity or related effects. For instance, because US EPA Integrated Risk Information System (IRIS) toxicological reviews also