Message

From: Vogel, Dana [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=8FA57C9380B2438895809B525DD668EA-DANA VOGEL]
Sent: 4/29/2015 9:05:34 PM
To: Anna Lowit [Lowit.Anna@epa.gov]
Subject: FW: IARC Glyphosate Discussion
Attachments: CompTox Evolution_NAS 21C RBE_April_2015_v2nc.pptx; WHO guidance - SOT poster - final.pdf; Judson et al 2011 Chem Res Tox High Throughput Risk Assessment.pdf; MAL Section 4-3-2ndDraft_R4.doc; Key Characteristics of Carcinogens_3-3-15.pdf

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From: Dix, David
Sent: Wednesday, April 29, 2015 5:04 PM
To: Housenger, Jack; Vogel, Dana; Rowland, Jess; Jordan, William; Smith, Charles; Miller, David
Subject: RE: IARC Glyphosate Discussion

Hello IARCians-

Here are all the documents I mentioned.

Jess, you will be at the June 2-9 meeting, right? As I mentioned, that wont be Ivan Rusyn and Matt Martin, this time it will be Ivan and David Reif (former EPA now NC State U).

It was and is fun, David

CompTox Evolution_NAS 2...

Rusty's presentation at NAS on working towards computational POD

WHO guidance - SOT poster - fina...

Probabilistic DR

Judson et al 2011 Chem Res Tox ...

High Throughput RA

MAL Section 4-3-2ndDraft_R4....

Key Characteristics o...

Using HTS in IARC cancer classifications

David J. Dix, Ph.D.
Director, Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency

1200 Pennsylvania Ave, NW (7201M)
Washington DC 20460

Email: dix.david@epa.gov
Office phone: 202-564-8429
Location: Room 4126A WJC East

-----Original Appointment-----
From: Housenger, Jack
Sent: Thursday, April 09, 2015 2:32 PM
To: Housenger, Jack; Dix, David; Vogel, Dana; Rowland, Jess; Jordan, William; Smith, Charles; Miller, David
Subject: IARC Glyphosate Discussion
When: Wednesday, April 29, 2015 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: PYS-12621

Message

From: Nguyen, Khue [Nguyen.Khue@epa.gov]
Sent: 2/18/2016 2:38:48 PM
To: Smith, Charles [Smith.Charles@epa.gov]; Perron, Monique [Perron.Monique@epa.gov]; Dunbar, Anwar [Dunbar.Anwar@epa.gov]; Bloem, Thomas [Bloem.Thomas@epa.gov]; Akerman, Gregory [Akerman.Gregory@epa.gov]
CC: Moriarty, Thomas [Moriarty.Thomas@epa.gov]
Subject: FW: Review in Environmental Health: Concerns over use of glyphosate
Attachments: Myers et al 2016.pdf

I am forwarding this to HED as an FYI. This is a review article that recently came out that filtered to me through various channels, including through Zen Honeycutt. Nothing new here, but thought you should know. Not sure if Dana Vogel already forwarded this.

Thanks,

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

From: Anderson, Neil
Sent: Thursday, February 18, 2016 8:38 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>
Subject: FW: Review in Environmental Health: Concerns over use of glyphosate

FYI

From: Goodis, Michael
Sent: Thursday, February 18, 2016 8:05 AM
To: Anderson, Neil <Anderson.Neil@epa.gov>
Subject: FW: Review in Environmental Health: Concerns over use of glyphosate

FYI

Michael L. Goodis, P.E.
Associate Director, Pesticide Re-evaluation Division (7508P)
Office of Pesticide Programs
US Environmental Protection Agency
Phone: 703-308-8157
goodis.michael@epa.gov

From: Keigwin, Richard
Sent: Wednesday, February 17, 2016 5:39 PM
To: Housenger, Jack <Housenger.Jack@epa.gov>; Monell, Marty <Monell.Marty@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>; Vogel, Dana <Vogel.Dana@epa.gov>

Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Goodis, Michael <Goodis.Michael@epa.gov>
Subject: Review in Environmental Health: Concerns over use of glyphosate

David Dix shared the attached with me. It is a consensus statement developed by:

John Peterson Myers, Michael N. Antoniou, Bruce Blumberg, Lynn Carroll, Theo Colborn, Lorne G. Everett, Michael Hansen, Philip J. Landrigan, Bruce P. Lanphear, Robin Mesnage, Laura N. Vandenberg, Frederick S. vom Saal, Wade V. Welshons and Charles M. Benbrook

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From: Dix, David
Sent: Wednesday, February 17, 2016 12:27 PM
To: Keigwin, Richard
Cc: Robbins, Jane
Subject: FW: Myers et al. article-Environmental Science

David J. Dix, Ph.D.
Director, Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (7201M)
Washington DC 20460

Email: dix.david@epa.gov
Office phone: 202-564-8429
Location: Room 4126A WJC East

From: Weber, Whitney
Sent: Wednesday, February 17, 2016 11:58 AM
To: Bailey, Laura <Bailey.Laura@epa.gov>; Knott, Steven <Knott.Steven@epa.gov>; Dix, David <Dix.David@epa.gov>
Subject: Myers et al. article-Environmental Science

Hello,

I have attached the Myers et al. article published today in Environmental Science.

Whitney Weber, MPH
Association of Schools and Programs of Public Health (ASPPH) Fellowship Program Participant
U.S. Environmental Protection Agency (EPA)
Office of Science Coordination and Policy (OSCP)
Office of Chemical Safety and Pollution Prevention (OCSPP)

Room 4106K WJC East
1200 Pennsylvania Ave, NW (7201M)
Washington DC 20460

Email: weber.whitney@epa.gov
Office Phone: 202-564-3097

Message

From: Perron, Monique [Perron.Monique@epa.gov]
Sent: 2/17/2016 1:50:11 PM
To: Akerman, Gregory [Akerman.Gregory@epa.gov]
Subject: FW: by 5 pm -- FW: LINDA ACTION: Interview/comment request
Attachments: 2016-0211 EH on roundup final proofs (1).pdf; ATT00001.htm

In case you're curious.

From: Smith, Charles
Sent: Wednesday, February 17, 2016 5:36 AM
To: Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>
Cc: Bloem, Thomas <Bloem.Thomas@epa.gov>
Subject: Fwd: by 5 pm -- FW: LINDA ACTION: Interview/comment request

Wow. Very thorough report. We should likely look at the points laid out and see where we agree, disagree, and if there are any we are unsure about.

Sent from my iPhone

Begin forwarded message:

> **From:** "Vogel, Dana" <Vogel.Dana@epa.gov>
> **Date:** February 16, 2016 at 4:38:44 PM EST
> **To:** "Smith, Charles" <Smith.Charles@epa.gov>, "Lowit, Anna" <Lowit.Anna@epa.gov>, "Rowland, Jess" <Rowland.Jess@epa.gov>, "Dawson, Jeffrey" <Dawson.Jeff@epa.gov>
> **Subject: FW: by 5 pm -- FW: LINDA ACTION: Interview/comment request**
>
> ---
>
> **From:** Housenger, Jack
> **Sent:** Tuesday, February 16, 2016 3:47 PM
> **To:** Vogel, Dana <Vogel.Dana@epa.gov>
> **Subject:** FW: by 5 pm -- FW: LINDA ACTION: Interview/comment request
>
> Is this what you were talking about?
>
> ---
>
> **From:** Strauss, Linda
> **Sent:** Tuesday, February 16, 2016 3:28 PM
> **To:** Housenger, Jack <Housenger.Jack@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
> **Subject:** by 5 pm -- FW: LINDA ACTION: Interview/comment request
>
> Jack, have we seen this from Environmental Health? Want to say this? Something else?

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:19 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: LINDA ACTION: Interview/comment request

More from the reporter:

Hi Robert, You are correct -- no EPA affiliated scientists. I reached out to the EPA for comment because this group of health scientists is calling on federal agencies, such as the EPA, to re-evaluate the safety and science of glyphosate. So, I wanted to provide a chance to respond to the suggestions from the report that current federal testing is inadequate and a re-evaluation is needed to ensure the health of people exposed to this ubiquitous herbicide.

The very latest you can get back to me? The story will be published tomorrow morning and I could get a response in anytime before 8 AM ET tomorrow I'd say.

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:06 PM
To: Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Lee, Monica <Lee.Monica@epa.gov>
Subject: MONICA/DALE/LINDA ACTION: Interview/comment request

+ Monica.

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:04 PM
To: Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: DALE/LINDA ACTION: Interview/comment request

All, I've told this reporter it's unlikely we can get him comment by this afternoon, as we need to review the attached document. Please advise on what you'd like to do. Do we have some general language on Glyphosate review?

I'm waiting to see whether he'll be revisiting the story and whether he can accept a response at a later date.

From: Milbourn, Cathy
Sent: Tuesday, February 16, 2016 1:54 PM
To: Daguillard, Robert <Daguillard.Robert@epa.gov>
Subject: Fwd: Interview/comment request

Hi Robert. Can you please take this one?

Sent from my iPhone

Begin forwarded message:

From: "BBienkowski@ehn.org" <BBienkowski@ehn.org>
To: "Milbourn, Cathy" <Milbourn.Cathy@epa.gov>
Subject: Interview/comment request

Good morning, Cathy. Brian, editor of Environmental Health News, here.

I am writing a story on deadline about a report to be released today at 7pm ET urging federal agencies to take a fresh look at the toxicology/biomonitoring efforts on glyphosate.

I've attached a copy of the review.

I was hoping someone at the EPA could chat with me about the review or comment on its suggestion that federal agencies need to play some catch up when it comes to monitoring the exposure/toxicity of glyphosate based herbicides.

Let me know what might work. Deadline is this afternoon.

Thanks!

Brian
--
Brian Bienkowski
Editor
Environmental Health News, The Daily Climate
Ex. 6 - Personal Privacy
Email: bbienkowski@ehn.org
Twitter: @BrianBienkowski

Appointment

From: Jones, Tawaunna [Jones.Tawaunna@epa.gov]
Sent: 11/4/2015 7:11:01 PM
To: Wise, Louise [Wise.Louise@epa.gov]; Mojica, Andrea [Mojica.andrea@epa.gov]; Burke, Thomas [Burke.Thomas@epa.gov]; Gentry, Nathan [Gentry.Nathan@epa.gov]; Smith, Kelley [Smith.Kelley@epa.gov]; Deener, Kathleen [Deener.Kathleen@epa.gov]; Jordan, William [Jordan.William@epa.gov]; Monell, Marty [Monell.Marty@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rowland, Jess [Rowland.Jess@epa.gov]; Lowit, Anna [Lowit.Anna@epa.gov]; Smith, Charles [Smith.Charles@epa.gov]; Morton, Thurston [Morton.Thurston@epa.gov]; Perron, Monique [Perron.Monique@epa.gov]; Dunbar, Anwar [Dunbar.Anwar@epa.gov]; Akerman, Gregory [Akerman.Gregory@epa.gov]; Bloem, Thomas [Bloem.Thomas@epa.gov]; Middleton, Karlyn [Middleton.Karlyn@epa.gov]; Dawson, Jeffrey [Dawson.Jeff@epa.gov]; Lobdell, Danelle [Lobdell.Danelle@epa.gov]; Wood, Charles [Wood.Charles@epa.gov]; Nguyen, Thuy [Nguyen.Thuy@epa.gov]; Dix, David [Dix.David@epa.gov]
CC: Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Venkateshwara, Lata [Venkateshwara.Lata@epa.gov]; Kavlock, Robert [Kavlock.Robert@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]; McQueen, Jacqueline [McQueen.Jacqueline@epa.gov]; Birchfield, Norman [Birchfield.Norman@epa.gov]; Cogliano, Vincent [cogliano.vincent@epa.gov]

Subject: Glyphosate Human Health meeting
Attachments: glyphosate tom burke briefing slide deck 11 4 15 aftn revised.pptx
Location: DCRoomRRB41213/ORD; call in Ex. 6 - Personal Privacy

Start: 11/5/2015 8:00:00 PM
End: 11/5/2015 9:00:00 PM
Show Time As: Tentative

glyphosate tom burke briefing sli...

Message

From: Nguyen, Khue [Nguyen.Khue@epa.gov]
Sent: 8/16/2017 10:31:11 PM
To: Perron, Monique [Perron.Monique@epa.gov]; Cook, Colwell [cook.colwell@epa.gov]; Dunbar, Anwar [Dunbar.Anwar@epa.gov]; Olinger, Christine [Olinger.Christine@epa.gov]; Akerman, Gregory [Akerman.Gregory@epa.gov]; Bloem, Thomas [Bloem.Thomas@epa.gov]; Becker, Jonathan [Becker.Jonathan@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Spatz, Dana [Spatz.Dana@epa.gov]; Louie-Juzwiak, Rosanna [Louie-Juzwiak.Rosanna@epa.gov]; Blankinship, Amy [Blankinship.Amy@epa.gov]; Hetrick, James [Hetrick.James@epa.gov]; Lowit, Anna [Lowit.Anna@epa.gov]
Subject: RE: glyphosate Q+A for AA confirmation
Attachments: Glyphosate updated Q+A for AA confirmation 8.16.17 evening after team comments.docx

FYI: this is the latest version of the glyphosate Q+A doc. **Ex. 5 - Deliberative Process**
Ex. 5 - Deliberative Process I'm going to be out rest of this week and all next week—but I think we are mostly set right now for the glyphosate Q+A

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

From: Nguyen, Khue
Sent: Tuesday, August 15, 2017 5:19 PM
To: Perron, Monique <Perron.Monique@epa.gov>; Cook, Colwell <cook.colwell@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>; Becker, Jonathan <Becker.Jonathan@epa.gov>; Berwald, Derek <Berwald.Derek@epa.gov>; Spatz, Dana <Spatz.Dana@epa.gov>; Louie-Juzwiak, Rosanna <Louie-Juzwiak.Rosanna@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>; Hetrick, James <Hetrick.James@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: glyphosate Q+A for AA confirmation

That's correct, only the questions are due this week. You have more time to review the answers.

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

From: Perron, Monique
Sent: Tuesday, August 15, 2017 5:16 PM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; Cook, Colwell <cook.colwell@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>; Becker, Jonathan <Becker.Jonathan@epa.gov>; Berwald, Derek <Berwald.Derek@epa.gov>; Spatz, Dana <Spatz.Dana@epa.gov>; Louie-Juzwiak, Rosanna <Louie-Juzwiak.Rosanna@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>; Hetrick, James

<Hetrick.James@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: glyphosate Q+A for AA confirmation

Hi Khue,

I'm okay with the list of questions. We are working on editing the answers and will need to send them through our management for review. I'm guessing we'll have more time for that now given only the questions are going to the IO on Friday. Is that correct?

Thanks,
Monique

From: Nguyen, Khue
Sent: Tuesday, August 15, 2017 3:37 PM
To: Cook, Colwell <cook.colwell@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>; Becker, Jonathan <Becker.Jonathan@epa.gov>; Berwald, Derek <Berwald.Derek@epa.gov>; Spatz, Dana <Spatz.Dana@epa.gov>; Louie-Juzwiak, Rosanna <Louie-Juzwiak.Rosanna@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>; Hetrick, James <Hetrick.James@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: glyphosate Q+A for AA confirmation

Hi folks,

We just heard from Yu-Ting on this. The Qs (not the answers themselves) for glyphosate need to be sent to the IO on Friday. I'm going to need folks to **review the Qs only for glyphosate** and give me **concurrence by 3pm this Wednesday, 8/16**. I'm out of the office on Thursday and Friday.

At some later point, we will prob circle back and ask you to review the actual answers to the questions.

Thanks,

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

From: Cook, Colwell
Sent: Monday, August 14, 2017 7:04 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>; Becker, Jonathan <Becker.Jonathan@epa.gov>; Berwald, Derek <Berwald.Derek@epa.gov>; Spatz, Dana <Spatz.Dana@epa.gov>; Louie-Juzwiak, Rosanna <Louie-Juzwiak.Rosanna@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>; Hetrick, James <Hetrick.James@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: glyphosate Q+A for AA confirmation

Khue – when do you need our comments?

Colwell

****
Colwell A. Cook, Ph.D.
Entomologist/Lead Biologist
EPA/OPP/BEAD
1200 Pennsylvania Ave. NW
Washington, DC 20460
phone: 703-308-8146
****

From: Nguyen, Khue
Sent: Friday, August 11, 2017 5:24 PM
To: Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Olinger, Christine <Olinger.Christine@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>; Becker, Jonathan <Becker.Jonathan@epa.gov>; Chism, William <Chism.Bill@epa.gov>; Berwald, Derek <Berwald.Derek@epa.gov>; Cook, Colwell <cook.colwell@epa.gov>; Spatz, Dana <Spatz.Dana@epa.gov>; Louie-Juzwiak, Rosanna <Louie-Juzwiak.Rosanna@epa.gov>; Blankinship, Amy <Blankinship.Amy@epa.gov>; Hetrick, James <Hetrick.James@epa.gov>; Venkateshwara, Lata <Venkateshwara.Lata@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: glyphosate Q+A for AA confirmation

Hi all,

Management asked us to pull together a Q+A doc for glyphosate in preparation for the AA's confirmation. We updated the older Q+A from fall 2015 and added some new questions on the cancer issue. This version has already been reviewed by Yu-Ting. Please take a quick look and send comments.

Most of the questions pertain to HED and the cancer issue. There is one question about WRM that BEAD should look at. Management wanted some tough questions, so we removed most of the background materials from the older version.

Thanks,

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

Message

From: Behl, Betsy [Behl.Betsy@epa.gov]
Sent: 9/20/2017 2:59:16 PM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Barone, Stan [Barone.Stan@epa.gov]
Subject: FW: Analysis that we just published "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?"
Attachments: Tox21 COCs Do Not Predict Cancer Becker et al 2017.pdf

You probably know about this already, but sending on just in case.

Best, Betsy

From: Becker, Rick [mailto:Rick_Becker@americanchemistry.com]
Sent: Wednesday, September 20, 2017 10:46 AM
To: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: Analysis that we just published "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?"

Dear Dr. Ramasamy and Behl,

I'd like to bring to your attention our recent paper "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?" It is an open access article and can be freely distributed to your EPA colleagues. A pdf version is attached. The paper can be accessed on line at http://www.sciencedirect.com/science/article/pii/S0273230017302714?via%3Dihub.

EPA IRIS seems to be adopting the IARC approach for using key characteristics of carcinogens (KCC) from high throughput screening (HTS) assays and other types of studies as mechanistic evidence for classification of chemicals. In essence, this approach is based on implied and unverified inference – that bioactivity detected in assays putatively measuring a KCC indicates high likelihood a substance is carcinogenic.

So we decided to explicitly test how well such HTS data predict cancer classifications. Substances that USEPA OPP previously classified as having cancer hazard potential were designated as positives and substances OPP determined do not pose a carcinogenic hazard were designated as negatives. We downloaded HTS (ToxCast/Tox21) data for these substances and then sorted the results into 7 KCC (data for the other 3 KCC were not available); we used the exact same approach for assigning assays to KCCs as IARC. We then analyzed the dataset using an extensive array of statistics and machine learning algorithms. We found that the ability to predict cancer hazard for each KCC, alone or in combination, was no better than chance. Thus, concluding there's little scientific confidence in inference models derived from current ToxCast/Tox21 assays for KCC to predict cancer. Accordingly, in the paper, we recommend an improved approach for integrating such mechanistic data in cancer evaluations. (Note: we cite the EPA Hill et al 2017 study, in which, although KCC's were not used, showed that neither all assays (HTS hits per chemical) nor HTS results for cancer-related assays were capable of distinguishing USEPA's "probable/likely" carcinogens from "not likely" carcinogens.)

Please don't hesitate to contact me if you have any questions on the analysis or conclusions reached in our publication.

Thanks

Richard A. Becker Ph.D. DABT | American Chemistry Council
Science and Research Division
rick_becker@americanchemistry.com
700 2nd Street, NE | Washington, DC | 20002
O: (202) 249-6405

www.americanchemistry.com

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Message

From: Vogel, Dana [Vogel.Dana@epa.gov]
Sent: 2/16/2016 9:38:44 PM
To: Smith, Charles [Smith.Charles@epa.gov]; Lowit, Anna [Lowit.Anna@epa.gov]; Rowland, Jess [Rowland.Jess@epa.gov]; Dawson, Jeffrey [Dawson.Jeff@epa.gov]
Subject: FW: by 5 pm -- FW: LINDA ACTION: Interview/comment request
Attachments: 2016-0211 EH on roundup final proofs (1).pdf; ATT00001.htm

---

From: Housenger, Jack
Sent: Tuesday, February 16, 2016 3:47 PM
To: Vogel, Dana <Vogel.Dana@epa.gov>
Subject: FW: by 5 pm -- FW: LINDA ACTION: Interview/comment request

Is this what you were talking about?

From: Strauss, Linda
Sent: Tuesday, February 16, 2016 3:28 PM
To: Housenger, Jack <Housenger.Jack@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
Subject: by 5 pm -- FW: LINDA ACTION: Interview/comment request

Jack, have we seen this from Environmental Health? Want to say this? Something else?

Ex. 5 - Deliberative Process

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:19 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: LINDA ACTION: Interview/comment request

More from the reporter:

Hi Robert, You are correct -- no EPA affiliated scientists. I reached out to the EPA for comment because this group of health scientists is calling on federal agencies, such as the EPA, to re-evaluate the safety and science of glyphosate. So, I wanted to provide a chance to respond to the suggestions from the report that current federal testing is inadequate and a re-evaluation is needed to ensure the health of people exposed to this ubiquitous herbicide.

The very latest you can get back to me? The story will be published tomorrow morning and I could get a response in anytime before 8 AM ET tomorrow I'd say.

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:06 PM
To: Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Lee, Monica <Lee.Monica@epa.gov>
Subject: MONICA/DALE/LINDA ACTION: Interview/comment request

+ Monica.

From: Daguillard, Robert
Sent: Tuesday, February 16, 2016 3:04 PM
To: Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: DALE/LINDA ACTION: Interview/comment request

All, I've told this reporter it's unlikely we can get him comment by this afternoon, as we need to review the attached document. Please advise on what you'd like to do. Do we have some general language on Glyphosate review?

I'm waiting to see whether he'll be revisiting the story and whether he can accept a response at a later date.

From: Milbourn, Cathy
Sent: Tuesday, February 16, 2016 1:54 PM
To: Daguillard, Robert <Daguillard.Robert@epa.gov>
Subject: Fwd: Interview/comment request

Hi Robert. Can you please take this one?

Sent from my iPhone

Begin forwarded message:

> **From:** "BBienkowski@ehn.org" <BBienkowski@ehn.org>
> **To:** "Milbourn, Cathy" <Milbourn.Cathy@epa.gov>
> **Subject: Interview/comment request**
>
> Good morning, Cathy. Brian, editor of Environmental Health News, here.
>
> I am writing a story on deadline about a report to be released today at 7pm ET urging federal agencies to take a fresh look at the toxicology/biomonitoring efforts on glyphosate.
>
> I've attached a copy of the review.
>
> I was hoping someone at the EPA could chat with me about the review or comment on its suggestion that federal agencies need to play some catch up when it comes to monitoring the exposure/toxicity of glyphosate based herbicides.
>
> Let me know what might work. Deadline is this afternoon.
>
> Thanks!
>
> Brian
> --
> Brian Bienkowski

Editor
Environmental Health News, The Daily Climate
(c) Ex. 6 - Personal Privacy
Email: bbienkowski@ehn.org
Twitter: @BrianBienkowski

Message

From: Knizner, Steve [Knizner.Steve@epa.gov]
Sent: 10/19/2015 1:59:54 PM
To: Dinkins, Darlene [Dinkins.Darlene@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: RE: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Flag: Follow up

Hi Darlene
Please just invite me – AD has no agenda items.
Thanks, Steve

From: Dinkins, Darlene
Sent: Monday, October 19, 2015 9:37 AM
To: OPP Division Directors & Associate Directors <OPP_Division_Directors__Associate_Directors@epa.gov>
Subject: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Good morning,

Please see below the agenda (with topic questions) for the meeting with the National Pesticide Reform Coalition (NGO) on Thursday, October 22, at 1:00 pm. Please let me know who from your staff you would like to invite to the meeting.

Darlene Dinkins
Office of Pesticide Programs
U.S. Environmental Protection Agency
(703) 305-5214

From: Cynthia Palmer [mailto:CPalmer@abcbirds.org]
Sent: Friday, October 16, 2015 8:54 PM
To: Dinkins, Darlene <Dinkins.Darlene@epa.gov>
Subject: draft agenda for Thursday's meeting

Hi Darlene,
Here is our draft agenda for Thursday's meeting with OPP leadership.
Please confirm that I have the correct call-in information for those not able to be there in person.
Thanks!!
Have a great weekend.
c.

National Pesticide Reform Coalition (NPRC) Meeting – Draft Agenda
Thursday, 22 October, 2015 at 1 p.m.
EPA - Potomac Yards South, 2777 Crystal Drive, Arlington, VA
Conference line:
Ex. 6 - Personal Privacy

Participants – waiting for others to confirm
American Bird Conservancy – Cynthia Palmer

California Rural Legal Assistance Foundation -- Anne Katten
Center for Biological Diversity -- Brett Hartl
Center for Food Safety – Peter Jenkins and Larissa Walker
Farmworker Association of Florida -- Jeannie Economos
Farmworker Justice -- Virginia Ruiz
Friends of the Earth -- Tiffany Finck-Haynes
Pesticide Action Network -- Emily Marquez
Pollinator Stewardship Council – Michele Colopy and Jeff Anderson
Northwest Center for Alternatives to Pesticides -- Sharon Selvaggio

Neonicotinoids (TFH, LW, PJ, MC, CP)

Many people were surprised when the PPDC Pollinator Subcommittee cancelled this week's meeting due to potential conflicts with NAPPC (North American Pollinator Protection Campaign) and HBHC (Honey Bee Health Coalition), as these represent outside institutions with their own separate agendas. Please explain how this decision came about.

Will the Ninth Circuit Court of Appeals decision on sulfoxaflor change the way other neonics are reviewed by EPA? If so, what changes might we expect for new registrations? For re-registrations?

What other neonics or neonic-like chemicals are coming down the pike for registration?

Please give us the latest estimate as to when we might expect to see the first round of registration review documents for imidacloprid and other neonicotinoids.

There is evidence that the EPA's aquatic reference levels for neonicotinoids are out of line with the science and with those used by other countries. How and when will EPA revise its aquatic benchmarks for the neonicotinoids?

Several new studies and reports raise major concerns about effects of neonicotinoids that EPA may have overlooked, including,

- Williams et al. Honey bee queens highly vulnerable to two neonicotinoid insecticides. *Scientific Reports* 5, Article number: 14621 (2015) doi:10.1038/srep14621
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- Limay-Rios et al. 2015 Neonicotinoid insecticide residues in soil dust and associated parent soil in fields with a history of seed treatment use on crops in Southwestern Ontario. Environ Toxicol Chem, Accepted manuscript. DOI 10:1002/etc. 3257.
- Center for Food Safety report, *Water Hazard: Aquatic Contamination by Neonicotinoid Insecticides in the United States*," which describes widespread ongoing neonicotinoid contamination in excess of safe levels.

Please indicate whether you will take regulatory action in response to these new indications of serious risks?

Please share with us your current thinking about the matter of re-characterizing neonicotinoid-coated seeds as pesticides under FIFRA, requiring fully enforceable label warnings and use directions for them, instead of exempting the coated seeds as a "treated article."

What progress can you report on EPA's planned completion of its coated seed efficacy assessment for corn and other crops? What is the proposed timeframe for the efficacy analyses on these other commodities? Have EPA plans been affected by the pushback from USDA?

Is EPA planning to remove the 88 active ingredients listed in the EPA document, *Mitigating Exposure from Acutely Toxic Pesticide Products* (docket EPA-HQ-OPP-2014-0818-0003) from all states that do not create State Pollinator Protection Plans?
Nearly all of the formulated products of these actives have bee hazard statements. The EPA action seems to imply that the current "do not apply to blooming crops or weeds if bees are actively visiting the treatment area" label is inadequate protection. This would suggest that all of those pesticides are mis-labeled and that the Administrator should issue a Stop Use Order.
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We applaud the efforts underway at EPA to improve its incident reporting systems. But without a biomarker, we will remain in the dark on neonic-related poisonings. We are hoping that the development of biomarkers will go hand in hand with incident reporting upgrades.
What progress has been made to develop a biomarker for neonicotinoid poisoning in birds? It should not be difficult to develop a binding assay for brain tissue.

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What are the anticipated timelines for initiating registration review on the conazole fungicides? The official schedule lists these in quarter #1.
We know that the conazole fungicides have interesting reproductive effects in avian species, and yet the field relevance of avian reproductive studies has never really been established (we don't measure the level of residue in the egg so we can't bridge the gap between the laboratory and the wild). We also know that the conazole fungicides are synergistic with other pesticides, especially as regards bee toxicity. How will these characteristics be considered in EPA's registration review?

Rodenticides (CP)
The d-CON settlement of May 30, 2014 halted distribution to retailers as of March 31, 2015. It is troubling to see that brodifacoum-based detail continues to be sold by nearly every major retail outlet.
-Can EPA do anything to get these dangerous products off store shelves?
-Do we have any indication of how much surplus was stockpiled prior to the December 2014 deadline on production?
-What patterns or changes (if any) can you see in the incident data for brodifacoum and other SGARS? For bromethalin or other d-CON replacements?

Herbicides (CP, BH)
Glyphosate, the key ingredient in more than 700 products worldwide, was designated in March as a probable human carcinogen by WHO's International Agency for Research on Cancer. But it appears that the US government has been moving in the other direction on glyphosate: raising the allowable tolerance limits, focusing on weed resistance plans so we can keep using massive amounts, and leaving glyphosate out of the last round of USDA food residue testing.

At our meeting with you last May, we learned that the IARC report will not impact EPA's findings. The IARC used different definitions, dose-response assessments, statistical significance, types of tumors, etc. We were told that EPA looked at the same data and is confident in its separate approach.
Last month, the state of California announced its intention to list glyphosate as a known carcinogen under Proposition 65, which requires the state to publish a list of chemicals that cause cancer, birth defects, or other reproductive harm.
Does the California decision have any bearing on EPA?
What is the expected timeline for EPA's risk assessment on glyphosate?

Likewise, how is the registration review coming along for atrazine? When should we expect to see the risk assessment for atrazine?

MBTA (BH, CP)
Please give us an update on the Migratory Bird Treaty Act MOU between EPA and FWS. Last we heard, the attorneys were "scrubbing it." Any insights on what changes have been made and when it will go into force?

New Avitrol label vs. RED (CP)
At our last meeting, we learned that EPA had just received a proposal from the Avitrol Registrant to address the discrepancy between the RED (Reregistration Eligibility Decision) and the label instructions for elevated sites. What changes have been made?
[Background: The new label for Avitrol (required as of Sept. 22, 2014) does not follow EPA's own directive in the 2007 Reregistration Eligibility Decision for the protection of non-target species. The label encourages users to bait at elevated sites, where feasible. And yet for those elevated applications, and for any uses that are not "in populated areas," the label omits to include the mitigation clearly identified in Table 14 of the RED, namely *that the authorized handler must stay on the site during the entire application period*.]

Worker Protection Standard (VR, JE, AK)
We are glad that EPA is moving forward on WPS implementation and note that cooperative agreements have already been awarded to NASDA Foundation, AFOP and a UC Davis/Oregon State collaboration. How is EPA going to make sure that these organizations 1) involve farmworker organizations and workers in development of materials and training programs; and 2) develop materials and programs that meet the needs of a workforce that is ethnically and geographically diverse, and working in many different crops?

Advocates have been disappointed by inadequate enforcement of the current WPS, including low penalties and advance notice of inspections. Going forward, how will EPA ensure that new protections (such as those pertaining to minimum age of pesticide handlers, annual safety training, REIs and anti-retaliation) are adequately enforced by states? What steps is EPA taking to monitor state enforcement actions?

International Trade
If ratified, how do the Trans-Pacific and Trans-Atlantic Trade agreements affect EPA autonomy and ability to effectively regulate pesticide use in the US? To what extent do these agreements force the US to follow the lowest-common-denominator approach to pesticide registrations, using the most lax standards of participating nations?

Message

From: Rusyn, Ivan [IRusyn@cvm.tamu.edu]
Sent: 3/20/2015 5:32:36 PM
To: Dix, David [Dix.David@epa.gov]
Subject: Fwd: IARC Monographs, Vol 112, TLO and mews piece
Attachments: News Item Monograph Volume 112.pdf; TLO_V112_PIIS1470204515701348.pdf

Ivan Rusyn, MD, PhD
Professor
Veterinary Integrative Biosciences
College of Veterinary Medicine and Biomedical Sciences
Texas A&M University
College Station, TX 77843-4458
Ph: (979) 458-9866

Sent via the Samsung Galaxy Note® 3

-------- Original message --------
From: Kurt Straif <StraifK@iarc.fr>
Date:03/20/2015 1:25 PM (GMT-05:00)
To: lin.fritschi@curtin.edu.au, h.kromhout@uu.nl, egeghy.peter@epa.gov, teresar66@gmail.com, isabelle.baldi@isped.u-bordeaux2.fr, blairkansas@aol.com, f.forastiere@deplazio.it, john.mclaughlin@oahpp.ca, a.mannetje@massey.ac.nz, rafaelc@mor.org.il, Sonia El-Zaemey <ElzaemeyS@fellows.iarc.fr>, Charlotte Le Cornet <LeCornetC@students.iarc.fr>, Maria Leon Roux <leonrouxm@iarc.fr>, GMC24@columbia.edu, jahnke@niehs.nih.gov, drjameson@embarqmail.com, sergi@ualberta.ca, frank.lecurieux@echa.europa.eu, martin.matt@epa.gov, cportier@mac.com, mross@cvm.msstate.edu, "Rusyn, Ivan" <IRusyn@cvm.tamu.edu>, lxzeise@gmail.com, Jiri Zavadil <ZavadilJ@iarc.fr>
Cc: imo-all@iarc.fr, Nicolas Gaudin <GaudinN@iarc.fr>
Subject: IARC Monographs, Vol 112, TLO and mews piece

Dear all,

Thank you again for your most important contributions to develop this IARC Monograph.
The TLO summary report (also accessible after free registration) and an IARC news piece are attached here.

Best regards,
Kurt

Kurt Straif, MD PhD MPH
Head IARC Monographs
International Agency for Research on Cancer
World Health Organization
150 cours Albert Thomas
69372 Lyon Cedex 08, France
Tel +33 (0)472 73 85 07 (PA)
Fax +33 (0)472 73 83 19
http://monographs.iarc.fr

Message

From: Dix, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=C8006C73E3D34BA4AF6BF16C1E85FDA7-DIX, DAVID]
Sent: 4/2/2015 4:10:17 PM
To: Housenger, Jack [Housenger.Jack@epa.gov]; Tina Bahadori [Bahadori.Tina@epa.gov]
Subject: FW: IARC Monographs, Vol 112, TLO and mews piece
Attachments: News Item Monograph Volume 112.pdf; TLO_V112_PIIS1470204515701348.pdf

Jim is up to speed on this.

David J. Dix, Ph.D.
Director, Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (7201M)
Washington DC 20460

Email: dix.david@epa.gov
Office phone: 202-564-8429
Location: Room 4126A WJC East

From: Rusyn, Ivan [mailto:IRusyn@cvm.tamu.edu]
Sent: Friday, March 20, 2015 1:33 PM
To: Dix, David
Subject: Fwd: IARC Monographs, Vol 112, TLO and mews piece

Ivan Rusyn, MD, PhD
Professor
Veterinary Integrative Biosciences
College of Veterinary Medicine and Biomedical Sciences
Texas A&M University
College Station, TX 77843-4458
Ph: (979) 458-9866

Sent via the Samsung Galaxy Note® 3

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From: Kurt Straif <StraifK@iarc.fr>
Date:03/20/2015 1:25 PM (GMT-05:00)
To: lin.fritschi@curtin.edu.au, h.kromhout@uu.nl, egeghy.peter@epa.gov, teresar66@gmail.com, isabelle.baldi@isped.u-bordeaux2.fr, blairkansas@aol.com, f.forastiere@deplazio.it, john.mclaughlin@oahpp.ca, a.mannetje@massey.ac.nz, rafaelc@mor.org.il, Sonia El-Zaemey <ElzaemeyS@fellows.iarc.fr>, Charlotte Le Cornet <LeCornetC@students.iarc.fr>, Maria Leon Roux <leonrouxm@iarc.fr>, GMC24@columbia.edu, jahnke@niehs.nih.gov, drjameson@embarqmail.com, sergi@ualberta.ca, frank.lecurieux@echa.europa.eu, martin.matt@epa.gov, cportier@mac.com, mross@cvm.msstate.edu, "Rusyn, Ivan" <IRusyn@cvm.tamu.edu>, lxzeise@gmail.com, Jiri Zavadil <ZavadilJ@iarc.fr>

Cc: imo-all@iarc.fr, Nicolas Gaudin <GaudinN@iarc.fr>
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Head IARC Monographs
International Agency for Research on Cancer
World Health Organization
150 cours Albert Thomas
69372 Lyon Cedex 08, France
Tel +33 (0)472 73 85 07 (PA)
Fax +33 (0)472 73 83 19
http://monographs.iarc.fr

Message

From: Perlis, Robert [Perlis.Robert@epa.gov]
Sent: 10/20/2015 8:03:47 PM
To: Knorr, Michele [knorr.michele@epa.gov]; Dyner, Mark [dyner.mark@epa.gov]; Huskey, Angela [Huskey.Angela@epa.gov]; Koch, Erin [Koch.Erin@epa.gov]
Subject: RE: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Just FYI – I usually attend these meetings, and I intend to go to this one as well…

Bob Perlis
Pesticides and Toxic Substances Law Office
Office of General Counsel
US EPA
(202) 564-5636

From: Knorr, Michele
Sent: Tuesday, October 20, 2015 12:27 PM
To: Dyner, Mark <dyner.mark@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Huskey, Angela <Huskey.Angela@epa.gov>; Koch, Erin <Koch.Erin@epa.gov>
Subject: RE: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Nothing to add.

Michele L. Knorr
Attorney
Pesticides and Toxics Law Office
Office of General Counsel
202-564-5631

From: Dyner, Mark
Sent: Monday, October 19, 2015 4:36 PM
To: Perlis, Robert <Perlis.Robert@epa.gov>; Knorr, Michele <knorr.michele@epa.gov>; Huskey, Angela <Huskey.Angela@epa.gov>; Koch, Erin <Koch.Erin@epa.gov>
Subject: FW: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Not sure who's planning to attend, but I've taken a crack at answering some of the Peter Jenkins' questions in the neonic section.

From: Laws, Meredith
Sent: Monday, October 19, 2015 3:53 PM
To: Knorr, Michele; Dyner, Mark; Koch, Erin
Subject: FW: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

OGC: please see below. **Ex. 5 - Deliberative Process, A/C**

Maybe you've already seen this but I wanted to make sure. I am out on Thursday so won't be able to make the meeting – but if you have concerns, please let Jack know.

Meredith

From: Lewis, Susan
Sent: Monday, October 19, 2015 2:24 PM
To: OPP RD Managers <OPP_RD_Managers@epa.gov>
Subject: FW: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Susan Lewis
Director, Registration Division
Office of Pesticide Program
U.S.E.P.A
703-308-8009

From: Dinkins, Darlene
Sent: Monday, October 19, 2015 9:37 AM
To: OPP Division Directors & Associate Directors <OPP_Division_Directors__Associate_Directors@epa.gov>
Subject: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

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Office of Pesticide Programs
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Thursday, 22 October, 2015 at 1 p.m.
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Ex. 6 - Personal Privacy

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Ex. 5 - Deliberative Process

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Ex. 5 - Deliberative Process

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[Background: The new label for Avitrol (required as of Sept. 22, 2014) does not follow EPA's own directive in the 2007 Reregistration Eligibility Decision for the protection of non-target species. The label encourages users to bait at elevated sites, where feasible. And yet for those elevated applications, and for any uses that are not "in populated areas," the label omits to include the mitigation clearly identified in Table 14 of the RED, namely *that the authorized handler must stay on the site during the entire application period*.]

Worker Protection Standard (VR, JE, AK)
We are glad that EPA is moving forward on WPS implementation and note that cooperative agreements have already been awarded to NASDA Foundation, AFOP and a UC Davis/Oregon State collaboration. How is EPA going to make sure that these organizations 1) involve farmworker organizations and workers in development of materials and training programs; and 2) develop materials and programs that meet the needs of a workforce that is ethnically and geographically diverse, and working in many different crops?

Advocates have been disappointed by inadequate enforcement of the current WPS, including low penalties and advance notice of inspections. Going forward, how will EPA ensure that new protections (such as those pertaining to minimum age of pesticide handlers, annual safety training, REIs and anti-retaliation) are adequately enforced by states? What steps is EPA taking to monitor state enforcement actions?

International Trade
If ratified, how do the Trans-Pacific and Trans-Atlantic Trade agreements affect EPA autonomy and ability to effectively regulate pesticide use in the US? To what extent do these agreements force the US to follow the lowest-common-denominator approach to pesticide registrations, using the most lax standards of participating nations?

Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 4/1/2016 12:02:04 PM
To: Ross, Matthew [MRoss@cvm.msstate.edu]; Ivan Rusyn Ex. 6 - Personal Privacy Lauren Zeise Ex. 6 - Personal Privacy Martin, Matt [Martin.Matt@epa.gov]; Egeghy, Peter [Egeghy.Peter@epa.gov]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Calaf, Gloria [gmc24@cumc.columbia.edu]
CC: Kurt Straif [StraifK@iarc.fr]; Dana Loomis [LoomisD@iarc.fr]
Subject: Glyphosate- information requests

Dear Vol 112 Working Group members,

It has been brought to our attention that two state universities in the US have received information requests, issued under US state open records laws, concerning the IARC evaluation of glyphosate. IARC is not in a position to offer legal advice to you or your institution concerning these requests. However, it is the position of IARC that all draft documents and materials prepared by the Working Group in advance of or during the in-person Monograph meeting are to be considered draft and deliberative. Working Group members prepare these materials on behalf of IARC, and not as part of their official employment duties for a state or federal institution, and IARC is the sole owner of all such materials. IARC does not encourage participants to retain working drafts of documents after the related Monograph has been published.

We hope this information is helpful to you.

With kind regards,
Kate

Kate Z. Guyton PhD DABT
Responsible Officer, Volume 112
Monographs Section
International Agency for Research on Cancer
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France
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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.

Message

From: Chris Portier Ex. 6 - Personal Privacy
Sent: 11/11/2015 12:57:27 PM
To: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Aaron Blair [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy .lebailly@baclesse.fr; jspinelli@bccrc.ca; ahsmith@berkeley.edu; johnni@cancer.dk; eero.pukkala@cancer.fi; Elizabeth Ward [elizabeth.ward@cancer.org]; Paul.Demers@cancercare.on.ca; amr2@cdc.gov; eaw0@cdc.gov; mda1@cdc.gov; paul.schulte@cdc.hhs.gov; eva.schernhammer@channing.harvard.edu; Francine.laden@channing.harvard.edu; dweisenburger@coh.org; ecardis@creal.cat
Subject: IARC Monograph on Glyphosate
Attachments: IARCWG112ResponseV3.docx; ATT00001.htm

Dear Colleagues,

For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)

RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 900 agents in the last few decades. The Monographs Programme evaluates chemicals, complex mixtures, occupational exposures, physical agents and biological agents, as well as personal habits. Monographs are written by a Working Group (WG) over a period of about 12 months to evaluate all of the scientific literature on a given substance and, through a transparent and rigorous process[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS </title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>], reach a decision on the degree to which the scientific literature supports the ability of that substance to cause cancer. For Monograph 112[ADDIN EN.CITE <EndNote><Cite><Author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans</Author><Year>2015</Year><RecNum>3933</RecNum><DisplayText>[2]</DisplayText><record><rec-number>3933</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1438346335">3933</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans,</author></authors><secondary-authors><author>IARC Monographs Program</author></secondary-authors></contributors><titles><title>Glyphosate</title><secondary-title>IARC Monogr Eval Carcinog Risks Hum</secondary-title><alt-title>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</alt-title></titles><periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></periodical><alt-periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></alt-periodical><pages>1-92</pages><volume>112</volume><keywords><keyword>Animals</keyword><keyword>Biological Markers</keyword><keyword>Carcinogenicity Tests</keyword><keyword>Carcinogens,

Environmental/*analysis/toxicity</keyword><keyword>Causality</keyword><keyword>Glyphosate</keyword><keyword>Herbicides</keyword><keyword>Environmental Exposure/adverse effects/*analysis/statistics & numerical data</keyword><keyword>Humans</keyword><keyword>Time Factors</keyword></keywords><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The WG concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they came available on July 29, 2015. On August 31, 2015, the German Federal Institute for Risk Assessment (BfR) completed an addendum[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2015</Year><RecNum>3962</RecNum><DisplayText>[3]</DisplayText><record><rec-number>3962</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652969">3962</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Assessment of IARC Monographies Volume 112 (2015): Glyphosate</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.bfr.bund.de/cm/343/behoerden-der-eu-mitgliedstaaten-bescheinigen-der-bfr-bewertung-der-iarc-monographie-zu-glyphosat-hohe-wissenschaftliche-qualitaet-und-aussagekraft.pdf</url></related-urls></urls></record></Cite></EndNote>] (the BfR Addendum) to the Draft Renewal Assessment Report[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2013</Year><RecNum>3964</RecNum><DisplayText>[4]</DisplayText><record><rec-number>3964</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653708">3964</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Renewal Assessment Report</title></titles><dates><year>2013</year></dates><urls><related-urls><url>http://dar.efsa.europa.eu/dar-web/provision</url></related-urls></urls></record></Cite></EndNote>] (RAR) for glyphosate. This addendum was leaked by the media[ADDIN EN.CITE <EndNote><Cite><Author>Das Erste</Author><Year>2015</Year><RecNum>3963</RecNum><DisplayText>[5]</DisplayText><record><rec-number>3963</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653250">3963</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Das Erste,</author></authors></contributors><titles><title>BfRBewertung zu Glyphosat</title></titles><dates><year>2015</year></dates><urls><related-

urls><url>http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html</url></related-urls></urls></record></Cite></EndNote>]. The Addendum draws a very different conclusion on the literature than did the IARC WG. We are seriously concerned about the scientific quality of the BfR Addendum and feel that it is misleading regarding the potential for a carcinogenic hazard from exposure to glyphosate. We are also concerned about some of the implications of the Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "limited evidence in humans for the carcinogenicity of glyphosate". In the IARC review process, this is defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] The BfR Addendum (p. ii) then characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and target the third argument for the end of our letter.

The finding of "limited evidence" by the IARC WG was for non-Hodgkins lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a very weak positive finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. The BfR refers to this study as "the most powerful study" and that it was negative for NHL.

Several theoretical limitations of case-control studies are laid out in epidemiology textbooks [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies [ADDIN EN.CITE <EndNote><Cite><Author>Rothman</Author><Year>2008</Year><RecNum>3978</RecNum><DisplayText>[7]</DisplayText><record><rec-number>3978</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1447240364">3978</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>Rothman, Kenneth J.</author><author>Greenland, Sander</author><author>Lash, Timothy L.</author></authors></contributors><titles><title>Modern epidemiology</title></titles><pages>x, 758 p.</pages><edition>3rd</edition><keywords><keyword>Epidemiology Statistical methods.</keyword><keyword>Epidemiology Research Methodology.</keyword><keyword>Epidemiology.</keyword><keyword>Epidemiologic Methods.</keyword></keywords><dates><year>2008</year></dates><pub-location>Philadelphia</pub-location><publisher>Wolters Kluwer Health/Lippincott Williams & Wilkins</publisher><isbn>9780781755641
0781755646</isbn><accession-num>14993679</accession-num><call-num>RA652.2.M3 R67 2008</call-num><urls><related-urls><url>Publisher description http://www.loc.gov/catdir/enhancements/fy0743/2007036316-d.html</url><url>Table of contents only http://www.loc.gov/catdir/enhancements/fy0828/2007036316-t.html</url></related-urls></urls></record></Cite></EndNote>]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study's strengths and weaknesses as well as the study order. This is key in determining whether the positive associations seen are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analysis cited in the IARC Monograph[ADDIN EN.CITE <EndNote><Cite><Author>Schinasi</Author><Year>2014</Year><RecNum>3966</RecNum><DisplayText>[8]</DisplayText><record><rec-number>3966</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446654328">3966</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schinasi, L.</author><author>Leon, M. E.</author></authors></contributors><auth-address>Section of Environment and Radiation, International Agency for Research on Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France. schinasil@fellows.iarc.fr.
Section of Environment and Radiation, International Agency for Research on Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France. leonrouxm@iarc.fr.</auth-address><titles><title>Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients:

a systematic review and meta-analysis</title><secondary-title>Int J Environ Res Public Health</secondary-title></titles><periodical><full-title>Int J Environ Res Public Health</full-title><abbr-1>International journal of environmental research and public health</abbr-1></periodical><pages>4449-527</pages><volume>11</volume><number>4</number><keywords><keyword>Agricultural Workers' Diseases/chemically induced/*epidemiology</keyword><keyword>Humans</keyword><keyword>Lymphoma, Non-Hodgkin/*epidemiology</keyword><keyword>Occupational Exposure/*adverse effects</keyword><keyword>Pesticides/*toxicity</keyword></keywords><dates><year>2014</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>1660-4601 (Electronic)
1660-4601 (Linking)</isbn><accession-num>24762670</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/24762670</url></related-urls></urls><custom2>PMC4025008</custom2><electronic-resource-num>10.3390/ijerph110404449</electronic-resource-num></record></Cite></EndNote>] and redone by the WG is an excellent example of an objective evaluation of the existence of a consistent positive trend; this meta-analysis showed a statistically significant association. The BfR provided no justification for their evaluation of "no consistent positive association".

The final BfR conclusion (p. 22) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS </title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>]. "Sufficient Evidence" means "that a causal relationship has been established" between glyphosate and NHL. The BfR conclusion can be rewritten to mean that the epidemiological data does not meet the criteria for "Sufficient Evidence" established by IARC. However, this says nothing about concern that would arise for an association that is not strong enough to be causal, but is strong enough that "that causality is credible" as does the IARC "Limited Evidence" category.

Evidence from Chronic Exposure Animal Studies

We are astonished by the conclusions of the BfR regarding the animal carcinogenicity data. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[ADDIN EN.CITE
<EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[9]</DisplayText><record><rec-number>3421</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>], a rare tumour. A significant positive trend means that as the exposure increases, the pattern seen in the data supports an increasing risk with increasing dose. No comparisons of any individual exposure group to the control group were significant. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[ADDIN EN.CITE
<EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNum><DisplayText>[10]</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1385988909">611</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>JCFA</author></authors></contributors><titles><title>Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-location><publisher>Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization</publisher><isbn>WHO Technical Series #884</isbn><urls></urls></record></Cite></EndNote>], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of islet cell adenomas in two studies in Sprague-Dawley rats[ADDIN EN.CITE ADDIN EN.CITE.DATA]. In one of these rat studies, thyroid adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mice studies examined and for benign tumors in 2 of the five rat studies examined. By the IARC review criteria[ADDIN EN.CITE
<EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-

number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>], the evidence in the mouse constitutes sufficient evidence in animals.

The BfR agreed, stating (p. 44) "it is obvious that IARC concludes on "sufficient evidence of carcinogenicity" because the criteria for this conclusion are fully met." The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>]). Based on the BfR Addendum, it seems there were 3 additional mouse studies and 2 additional rat studies where they had sufficient evidence to review the findings. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[ADDIN EN.CITE <EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sugimoto</author></authors></contributors><titles><title>18-Month Oral Oncogenicity Study in Mice</title><secondary-title>Unpublished, designated ASB2012-11493 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ASB2012-11493 in BfR RAR</full-title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>], and one in Swiss-Webster mice[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2001</Year><RecNum>3969</RecNum><DisplayText>[15]</DisplayText><record><rec-number>3969</rec-

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ABS2012-11491 in BfR RAR</full-
title></periodical><dates><year>2001</year></dates><urls></urls></record></Cite
></EndNote>]. One of these studies[ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-
number><foreign-keys><key app="EN" db-
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RAR</full-
title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite
></EndNote>] also reported a positive trend for hemangiosarcoma. Moreover, BfR
reported two studies in CD-1 mice showing significant trends for malignant lymphoma[
ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
RecNum><DisplayText>[14, 16]</DisplayText><record><rec-number>3968</rec-
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RAR</secondary-title></titles><periodical><full-title>Unpublished, designated
ABS2012-11492 in BfR RAR</full-

title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. For all of the tumors described above in CD-1 mice, a positive trend was seen against the concurrent control.

However, in all cases in CD-1 mice, including those observed by the IARC, the BfR dismisses the observed trends in tumour incidence because there are no individual treatment groups which are significantly different from controls and because the maximum observed response is within the range of the historical control data (Table 5.3-1 in the Addendum). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[1, 17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>], scientific reports[ADDIN EN.CITE <EndNote><Cite><Year>2014</Year><RecNum>3977</RecNum><DisplayText>[18]</DisplayText><record><rec-number>3977</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1447173158">3977</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>NRC Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens,</author></authors></contributors><titles><secondary-title>Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary</secondary-title></titles><dates><year>2014</year></dates><pub-location>Washington (DC)</pub-location><publisher>National Academies Press</publisher><isbn>9780309301787
0309301785</isbn><accession-num>25232634</accession-num><urls><related-

urls><url>http://www.ncbi.nlm.nih.gov/pubmed/25232634</url></related-urls></urls><language>eng</language></record></Cite></EndNote>] and publications[ADDIN EN.CITE ADDIN EN.CITE.DATA] on the issue, the first choice should be the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, it should be from the same timeframe for the exact strain, preferably from the same laboratory or the same supplier and preferably with the same pathologist[ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>]. This was not the case for the historical control database used by BfR. One of the mouse studies[ADDIN EN.CITE <EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[9]</DisplayText><record><rec-number>3421</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>] was clearly done before this historical control database was developed, one study[ADDIN EN.CITE <EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal

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RAR</full-
title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite
></EndNote>] used Crj:CD-1 mice rather than Crl:CD-1 mice, and 1 study[ADDIN
EN.CITE
<EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNu
m><DisplayText>[10]</DisplayText><record><rec-number>611</rec-
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es><title>Evaluation of certain food additives and contaminants: Forty-ninth report of
the Joint FAO/WHO Expert Committee on Food
Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-
dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-
location><publisher>Joint Committee on Food Additives (including C. Portier), World
Health Organization/Food and Agriculture Organization</publisher><isbn>WHO
Technical Series #884</isbn><urls></urls></record></Cite></EndNote>] did not
specify the substrain and was reported in 1993 (probably started prior to 1988); hence
only a single study [ADDIN EN.CITE
<EndNote><Cite><Author>Unknown</Author><Year>2009</Year><RecNum>3970</
RecNum><DisplayText>[16]</DisplayText><record><rec-number>3970</rec-
number><foreign-keys><key app="EN" db-
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ABS2012-11492 in BfR RAR</full-
title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite
></EndNote>] used the right strain, but was reported more than 10 years after the
historical control dataset was developed. Interestingly, the historical control data used
by the BfR [ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</Rec
Num><DisplayText>[22]</DisplayText><record><rec-number>3975</rec-
number><foreign-keys><key app="EN" db-
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M.</author><author>Clifford,
C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions

in the CrI:CD-1(ICR)BR
Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River
Laboratories</publisher><urls><related-
urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_
mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] was from
studies in 7 laboratories using the Charles River Laboratory CD1 mice. Surprisingly,
there is a second report [ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</Rec
Num><DisplayText>[23]</DisplayText><record><rec-number>3976</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446660642">3976</key></foreign-keys><ref-type
name="Report">27</ref-type><contributors><authors><author>Giknis,
M.</author><author>Clifford,
C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions
in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year
Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River
Laboratories</publisher><urls><related-
urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_m
ouse.aspx</url></related-urls></urls></record></Cite></EndNote>] by the same
authors with a larger control database using the same mouse strain from 11
laboratories over the same time period (1987-2000) showing very different results. For
example, the 2000 publication[ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</Rec
Num><DisplayText>[22]</DisplayText><record><rec-number>3975</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446660626">3975</key></foreign-keys><ref-type
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Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River
Laboratories</publisher><urls><related-
urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_
mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows 5 and 4
studies out of 46 with adenomas (no more than 2 in any one study) and
adenocarcinomas (one in each study) respectively whereas the 2005 report[ADDIN
EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</Rec
Num><DisplayText>[23]</DisplayText><record><rec-number>3976</rec-
number><foreign-keys><key app="EN" db-
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name="Report">27</ref-type><contributors><authors><author>Giknis,
M.</author><author>Clifford,
C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions
in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year

Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows only 1 study each out of 54 studies with a single adenoma and a single adenocarcinoma; all other studies had no tumors.

Given this evidence, it is hard to perceive how the BfR reached the conclusion they provided. By their own evaluation, there were seven (7) positive findings in mice with three replicates for one tumor type and 2 positive findings for carcinomas in rats. After discarding the inappropriate use of historical evidence, it is no longer scientifically justifiable to refer to all of these studies as negative.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that the evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews use only publicly available data. Thus it is impossible for any scientists not associated with BfR to review this conclusion with any degree of scientific certainty. On the other hand, the BfR did not include evidence from exposed humans that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but do not agree that this is strong support for an oxidative stress mechanism. They reduce the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we would encourage the BfR to carefully review this science.

Finally, we strongly disagree that literature data should automatically receive less weight than guideline studies; once a chemical is on the market, the majority of the research done on that chemical will be done by very competent research laboratories that will use unique models to address specific issues related to toxicity that will not have guidelines associated with them. These have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of that data and a rigorous review of the findings. One important aspect of this process is transparency and on the ability to question the findings of others. This insures the credibility of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exists for the BfR RAR [ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2013</Year><RecNum>3964</RecNum><DisplayTex t>[4]</DisplayText><record><rec-number>3964</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653708">3964</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Renewal Assessment Report</title></titles><dates><year>2013</year></dates><urls><related-urls><url>http://dar.efsa.europa.eu/dar-web/provision</url></related-urls></urls></record></Cite></EndNote>] or the Addendum[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2015</Year><RecNum>3962</RecNum><DisplayTex t>[3]</DisplayText><record><rec-number>3962</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652969">3962</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Assessment of IARC Monographies Volume 112 (2015): Glyphosate</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.bfr.bund.de/cm/343/behoerden-der-eu-mitgliedstaaten-bescheinigen-der-bfr-bewertung-der-iarc-monographie-zu-glyphosat-hohe-wissenschaftliche-qualitaet-und-aussagekraft.pdf</url></related-urls></urls></record></Cite></EndNote>]. There are no authors or contributors listed for either document, a requirement for virtually all scientific papers. Citations for almost all of the references, even those from the open scientific literature, have been redacted from the documents. The ability to objectively evaluate the findings of a scientific report requires a complete list of the supporting evidence.

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Guidelines have been devised for analyzing carcinogenicity data developed after careful consideration of scientists on a global basis. One of the most widely cited is [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-

type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>] which is cited in the BfR Addendum. This document gives guidance on the analysis of carcinogenicity studies in contradiction to the methods used by the BfR. Thus, BfR uses the concept of guidelines to rule out the substantive inclusion of literature data into their risk assessment, but ignores guidelines when it comes to the use of historical controls and trend analyses.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A. In their 2013 Draft RAR, BfR concluded (Vol. 1, p. 139) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential". How is this possible? Consider the evidence and the conclusions.

The IARC WG saw an association between NHL and glyphosate in the human evidence, but could not rule out chance, bias and confounding; the IARC definition of "limited evidence"[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] for epidemiological data. BfR agreed, noting that other IARC categories are "not suitable". However the BfR concluded that an association was seen but dismissed it as insufficiently consistent.

The IARC WG saw significant effects for two tumors in two mouse studies and benign tumors in two rat studies. The BfR confirmed the statistically significant findings by the IARC WG, and agreed that the IARC criteria of "sufficient" evidence in animals is "fully met". BfR went on to identify two more mouse studies with kidney tumors, a second mouse study with an increase in hemangiosarcoma, and two

mouse studies showing increases in malignant lymphoma. Thus, all five mouse studies examined by the BfR were positive in at least 1 tumor site, 1 was positive in 3 tumor sites. Then using an inappropriate historical control dataset in an inappropriate way, dismiss all of these findings as chance.

The IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available data, including data on DNA damage in blood of exposed humans. The BfR, while confirming the positive studies seen for genotoxicity dismissed them all because they were not guideline studies and because, in their interpretation, all of the guideline assays were negative. The BfR confirmed the positive studies seen for oxidative stress, noted some concern over these data, but concluded they could not use them because there were no other data to support a finding of carcinogenicity or genotoxicity and the mechanism cannot stand alone.

We feel that the scientific arguments supporting the BfR review of the human, animal and mechanistic evidence is fundamentally flawed and should be rejected. We are concerned that this evaluation appears to have been designed to achieve a pre-determined goal rather than an objective scientific review. Finally, we strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide.

[ADDIN EN.REFLIST]

Message

From: Consolato Sergi Ex. 6 - Personal Privacy
Sent: 11/9/2015 6:34:12 PM
To: Kromhout, J. (Hans) [h.kromhout@uu.nl]
CC: Chris Portier [cportier@mac.com]; Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Aaron Blair [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy Kate Guyton [GuytonK@iarc.fr]
Subject: Re: IARC Monograph vol 112- EFSA Review of Glyphosate
Attachments: IARCWG112ResponseV2_Sergi.docx

Hi Chris,
I agree with Hans. However, please read my changes (track changes).
I reviewed the style, because we need to show our academic superior peer-review process, not just arguing, in my opinion
and how the process is.
Please let me know, what you think.
I would suggest to target Lancet Oncology or Science first
Another option may be Scientific Reports.
Best,
Consolato

On Mon, Nov 9, 2015 at 8:35 AM, Kromhout, J. (Hans) <h.kromhout@uu.nl> wrote:

Hi Chris,

You did a great job and I'm more than willing to be a co-author of the letter.

Best, Hans

From: Chris Portier Ex. 6 - Personal Privacy
Sent: Monday, November 09, 2015 12:05 PM
To: Isabelle Baldi; Aaron Blair; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise
Cc: Kate Guyton
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate

Dear all,

This week, the European Food Safety Agency (EFSA) will release their reassessment of glyphosate. In this review, they will conclude that glyphosate has no carcinogenic potential. This creates two problems as I see it. The first is that this wekens the strength of the IARC Monograph Program to stimulate change in how some of these agents are reviewed and addressed. The second is that it suggests we did not do our assessment adequately and that, had we seen all of the data they saw, we would have gotten a different answer. I do not intend to let this happen.

The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. This report was drafted prior to the IARC review. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. I have decided to draft a letter that I intend to try to get published in Carcinogenesis that addresses the points made by the BfR in their review. Failing my ability to get this into Carcinogenesis, EHP or some other Journal, I intend to send it as an open letter to the European Commission. I am enclosing both the BfR Addendum and my response for you to look over. I would like as many members of the Working Group to be co-authors on this as possible. If you wish to see changes made to the letter I can certainly work on that. If you are uncomfortable signing on to such a letter, I can appreciate that as in my previous job this would have been impossible. Please let me know by Friday November 13 if you can or cannot join me in this endeavor.

Sincerely,

Christopher Portier

--

Consolato Maria Sergi, MSc, MD, PhD, FRCPC
Professor of Pathology and Adj. Professor of Pediatrics
Dept. of Lab. Med. & Pathology (5B4.09), Univ. of Alberta, 8440 112 St, NW, Edmonton, AB, T6G 2B7, Canada
e-mail1: Ex. 6 - Personal Privacy e-mail2: sergi@ualberta.ca / (http://www.med.ualberta.ca/)
Tel. +1.780.407.7951 (Office - Direct Line) Tel. Ex. 6 - Personal Privacy / Pager Ex. 6 - Personal Privacy
Fax. +1.780.407.3009 (U of A Departmental Fax) / Prof. Networks: LinkedIn, ResearchGate
WARNING / DISCLAIMER >>> ALL COMMUNICATIONS ARE ENCRYPTED USING HTTPS and this email and any files transmitted with it are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you have received this email in error please notify the system manager. This message contains confidential information and is intended only for the individual named. If you are not the named addressee you should not disseminate, distribute or copy this e-mail. Please notify the sender immediately by e-mail if you have received this e-mail by mistake and delete this e-mail from your system. If you are not the intended recipient you are notified that disclosing, copying, distributing or taking any action in reliance on the contents of this information is strictly prohibited.

The International Agency for Research on Cancer (I.A.R.C.) Monographs Programme pinpoints and evaluates environmental causes of cancer in humans and has identified more than 900 agents in the last few decades. The Monographs Programme evaluates chemicals, complex mixtures, occupational exposures, physical agents and biological agents, as well as personal habits. The Monographs are written by a Working Group (WG) over a period of about 12 months to evaluate all of the scientific literature published on several and different scientific databases on a given substance or molecule and, through a transparent and rigorous anonymous peer-review process[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>]., Each WG member has a specific task to accomplish in writing up a report evaluating some literature data according to the competency and credentials. The peer-referee is indeed one of the WG, but he or she is not known to the author of report specific for the area of the competency. The double-blind review process is well standardized in academic institutions. Anonymity ensures the integrity and honesty of the system and provides faculties coming from different backgrounds more opportunity in their scientific and academic endeavors. Moreover, the peer-review includes avoidance of interpersonal conflicts and avoidance of political issues. Monographs' goal is to reach a decision on the degree to which the scientific literature supports the ability of that substance to cause cancer. For Monograph 112[ADDIN EN.CITE <EndNote><Cite><Author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans</Author><Year>2015</Year><RecNum>3933</RecNum><DisplayText>[2]</DisplayText><record><rec-number>3933</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1438346335">3933</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans,</author></authors><secondary-authors><author>IARC Monographs Program</author></secondary-authors></contributors><titles><title>Glyphosate</title><secondary-title>IARC Monogr Eval Carcinog Risks Hum</secondary-title><alt-title>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization,

International Agency for Research on Cancer</alt-title></titles><periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></periodical><alt-periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></alt-periodical><pages>1-92</pages><volume>112</volume><keywords><keyword>Animals</keyword><keyword>Biological Markers</keyword><keyword>Carcinogenicity Tests</keyword><keyword>Carcinogens, Environmental/*analysis/toxicity</keyword><keyword>Causality</keyword><keyword>Glyphosate</keyword><keyword>Herbicides</keyword><keyword>Environmental Exposure/adverse effects/*analysis/statistics & numerical data</keyword><keyword>Humans</keyword><keyword>Time Factors</keyword></keywords><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The WG concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and lead to a careful evaluation of the IARC monograph results when they came available on July 29, 2015. On August 31, 2015, the German Federal Institute for Risk Assessment (BfR) completed an addendum[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2015</Year><RecNum>3962</RecNum><DisplayText>[3]</DisplayText><record><rec-number>3962</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652969">3962</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Assessment of IARC Monographies Volume 112 (2015): Glyphosate</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.bfr.bund.de/cm/343/behoerden-der-eu-mitgliedstaaten-bescheinigen-der-bfr-bewertung-der-iarc-monographie-zu-glyphosat-hohe-wissenschaftliche-qualitaet-und-aussagekraft.pdf</url></related-urls></urls></record></Cite></EndNote>] (the BfR Addendum) to the Draft Renewal Assessment Report[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2013</Year><RecNum>3964</RecNum><DisplayText>[4]</DisplayText><record><rec-number>3964</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653708">3964</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Renewal Assessment

Report</title></titles><dates><year>2013</year></dates><urls><related-urls><url>http://dar.efsa.europa.eu/dar-web/provision</url></related-urls></urls></record></Cite></EndNote>] (RAR) for glyphosate. This addendum was leaked by the media[ADDIN EN.CITE <EndNote><Cite><Author>Das Erste</Author><Year>2015</Year><RecNum>3963</RecNum><DisplayText>[5]</DisplayText><record><rec-number>3963</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653250">3963</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Das Erste,</author></authors></contributors><titles><title>BfRBewertung zu Glyphosat</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html</url></related-urls></urls></record></Cite></EndNote>]. This ~~letter~~ communication is in response to the BfR Addendum and all co-~~signatories~~ authors of this ~~letters~~ communication are ~~were~~ members of the IARC WG for Monograph 112.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "limited evidence in humans for the carcinogenicity of glyphosate". In the IARC review process, this is defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] The BfR Addendum (p. ii) then characterizes the IARC interpretation as "precautionary" and takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two

arguments here and target the third argument ~~for~~ at the end of ~~our~~ this ~~letter~~communication.

The finding of "limited evidence" by the IARC WG was for non-Hodgkins lymphoma (NHL). When done correctly, cohort studies are very important in determining the carcinogenicity of an agent because they generally have less chance for bias, confounding and ~~missclassification~~misclassification than case-control studies. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The BfR refers to this study as "the most powerful study" and that it was negative for NHL. The study had a very weak positive finding for NHL (RR 1.1~~,~~; 0.7-1.9) with no apparent exposure response in the results. Had this been the only study available, the WG would certainly not have classified glyphosate as "limited evidence".

The potential limitations with case-control studies can be found in ~~any competent~~numerous ~~epidemiology~~ textbooks of epidemiology [ADDIN EN.CITE <EndNote><Cite><Author>Checkoway</Author><Year>2004</Year><RecNum>3965</RecNum><DisplayText>[6]</DisplayText><record><rec-number>3965</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446654137">3965</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>Checkoway, Harvey</author><author>Pearce, Neil</author><author>Kriebel, David</author></authors></contributors><titles><title>Research methods in occupational epidemiology</title><secondary-title>Monographs in epidemiology and biostatistics</secondary-title></titles><pages>xiv, 372 p.</pages><number>34</number><edition>2nd</edition><keywords><keyword>Occupational diseases Epidemiology.</keyword><keyword>Epidemiologic Methods.</keyword><keyword>Occupational Exposure.</keyword><keyword>Risk Assessment.</keyword></keywords><dates><year>2004</year></dates><pub-location>New York</pub-location><publisher>Oxford University Press</publisher><isbn>0195092422 (cloth alk. paper)</isbn><accession-num>13187775</accession-num><call-num>RC964 .C42 2004</call-num><urls><related-urls><url>Table of contents only http://www.loc.gov/catdir/toc/fy043/2003053095.html</url><url>Publisher description http://www.loc.gov/catdir/enhancements/fy0614/2003053095-d.html</url></related-urls></urls></record></Cite></EndNote>]. ~~and the~~The BfR uses these limitations to list all of the case-control studies as unreliable. This gives the impression to the public audience that all of the studies are equal in quality and unusable for an overall evaluation. However, in our opinion, ~~This~~ this is not the case. An IARC WG carefully evaluates all of the available epidemiology data until the date of the final meeting, looking at the study's strengths and weaknesses using a rigorous academic SWOT analysis of the papers as well as the study order. In our opinion, ~~This~~ this is ~~key~~ paramount in determining whether the positive associations seen, are a truly reliable indication of an association or simply a chance finding. All statistical evaluations are routinely performed using the raw data and/or supplementary data when available at time of the peer-review and final discussion. A highly competent statistic and epidemiologic service is provided as support to the WG members. Finally,

the meta-analysis cited in the IARC Monograph[ADDIN EN.CITE <EndNote><Cite><Author>Schinasi</Author><Year>2014</Year><RecNum>3966</RecNum><DisplayText>[7]</DisplayText><record><rec-number>3966</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446654328">3966</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schinasi, L.</author><author>Leon, M. E.</author></authors></contributors><auth-address>Section of Environment and Radiation, International Agency for Research on Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France. schinasil@fellows.iarc.fr.
Section of Environment and Radiation, International Agency for Research on Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France. leonrouxm@iarc.fr.</auth-address><titles><title>Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis</title><secondary-title>Int J Environ Res Public Health</secondary-title></titles><periodical><full-title>Int J Environ Res Public Health</full-title><abbr-1>International journal of environmental research and public health</abbr-1></periodical><pages>4449-527</pages><volume>11</volume><number>4</number><keywords><keyword>Agricultural Workers' Diseases/chemically induced/*epidemiology</keyword><keyword>Humans</keyword><keyword>Lymphoma, Non-Hodgkin/*epidemiology</keyword><keyword>Occupational Exposure/*adverse effects</keyword><keyword>Pesticides/*toxicity</keyword></keywords><dates><year>2014</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>1660-4601 (Electronic)
1660-4601 (Linking)</isbn><accession-num>24762670</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/24762670</url></related-urls></urls><custom2>PMC4025008</custom2><electronic-resource-num>10.3390/ijerph110404449</electronic-resource-num></record></Cite></EndNote>] and redone by the WG is the best method for evaluating if there is a consistent positive trend; ~~this~~ The meta-analysis showed indeed a statistically significant association. The BfR concludes (p. 22) "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate". We agree, but still consider that an association is observed, that causality is credible and that these findings should be used as part of the overall evaluation. This is particularly awkward, in consideration that several members of the IARC WG committee are academic faculties and/or editors in chief/editorial board members of high impact factor journals.

Evidence from Chronic Exposure Animal Studies

We are astonished by the conclusions of the BfR regarding the animal carcinogenicity data. In the IARC WG review, we found a significant positive trend for renal tumors in CD-1 mice[ADDIN EN.CITE <EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[8]</DisplayText><record><rec-number>3421</rec-

number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>]. ~~and s~~Since this entity ~~was~~ is, indeed, a rare tumor, compared ~~it~~ to an appropriate historical control dataset[ADDIN EN.CITE <EndNote><Cite><Author>Chandra</Author><Year>1994</Year><RecNum>3967</RecNum><DisplayText>[9]</DisplayText><record><rec-number>3967</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446654529">3967</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chandra, M.</author><author>Frith, C. H.</author></authors></contributors><auth-address>Experimental Pathology Department, American Cyanamid Company, Little Rock, Arkansas.</auth-address><titles><title>Spontaneous renal lesions in CD-1 and B6C3F1 mice</title><secondary-title>Exp Toxicol Pathol</secondary-title></titles><periodical><full-title>Exp Toxicol Pathol</full-title></periodical><pages>189-98</pages><volume>46</volume><number>3</number><keywords><keyword>Adenoma/pathology/veterinary</keyword><keyword>Animals</keyword><keyword>Carcinoma, Renal Cell/pathology/veterinary</keyword><keyword>Female</keyword><keyword>Kidney Diseases/pathology/*veterinary</keyword><keyword>Kidney Neoplasms/pathology/*veterinary</keyword><keyword>Male</keyword><keyword>Mice</keyword><keyword>*Mice, Inbred Strains</keyword><keyword>Rodent Diseases/*pathology</keyword></keywords><dates><year>1994</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0940-2993 (Print)
0940-2993 (Linking)</isbn><accession-num>8000238</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/8000238</url></related-urls></urls><electronic-resource-num>10.1016/S0940-2993(11)80080-1</electronic-resource-num></record></Cite></EndNote>] for CD-1 mice, it highlights ~~demonstrating~~ an even greater significance. A significant positive trend means that as the exposure increases, the pattern seen in the data supports an increasing risk with increasing dose. There were no significant comparisons of any individual exposure group to the control group, however the high exposure group was highly significantly different from the historical control population. We also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[ADDIN EN.CITE

<EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNum><DisplayText>[10]</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1385988909">611</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>JCFA</author></authors></contributors><titles><title>Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-location><publisher>Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization</publisher><isbn>WHO Technical Series #884</isbn><urls></urls></record></Cite></EndNote>], again with no individual exposure group significantly different from controls. Finally, we also ~~saw~~ pinpointed a significant increase in the incidence of islet cell adenomas in two studies in Sprague-Dawley rats[ADDIN EN.CITE ADDIN EN.CITE.DATA]. In one of these rat studies, thyroid adenomas in females and liver cell adenomas in males were also increased. Thus, in our opinion, there is frank evidence that glyphosate was positive for malignant tumors in both of the mice studies we examined and for benign tumors in two~~2~~ out of ~~the~~ five rat studies we examined. By the IARC review criteria[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>], the evidence in the mouse constitutes sufficient evidence in animals. The BfR agreed, stating (p. 44) "it is obvious that IARC concludes on "sufficient evidence of carcinogenicity" because the criteria for this conclusion are fully met."

It was clear at the time of our review that other studies had been done, but they were not publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type>

type><contributors><authors><author>IARC</author></authors><secondary-
authors><author>IARC Monographs</author></secondary-
authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS
</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-
location>Lyon, France</pub-location><urls><related-
urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></rel
ated-urls></urls></record></Cite></EndNote>]). Based on the BfR Addendum, it seems there were 3 additional mouse studies and 2 additional rat studies where they had sufficient evidence to review the findings. Remarkably, the findings of these studies independently replicated the studies reported in the Monograph. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal
Article">17</ref-
type><contributors><authors><author>Sugimoto</author></authors></contributors
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RAR</full-
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></EndNote>], and one in Swiss-Webster mice[ADDIN EN.CITE
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mice</title><secondary-title>unpublished, designated ABS2012-11491 in BfR
RAR</secondary-title></titles><periodical><full-title>unpublished, designated
ABS2012-11491 in BfR RAR</full-
title></periodical><dates><year>2001</year></dates><urls></urls></record></Cite
></EndNote>]. One of these studies[ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-
number><foreign-keys><key app="EN" db-
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type><contributors><authors><author>Sugimoto</author></authors></contributors
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title></titles><periodical><full-title>Unpublished, designated ASB2012-11493 in BfR

RAR</full-
title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite
></EndNote>] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant lymphoma[ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
RecNum><DisplayText>[14, 16]</DisplayText><record><rec-number>3968</rec-
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RAR</full-
title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite
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type><contributors><authors><author>Unknown</author></authors></contributors
><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the
Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR
RAR</secondary-title></titles><periodical><full-title>Unpublished, designated
ABS2012-11492 in BfR RAR</full-
title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite
></EndNote>]. For all of the tumors described above in CD-1 mice, a positive trend was seen against the concurrent control.

However, in all cases in CD-1 mice, including those observed by the IARC, the BfR dismisses the observed ~~tumors because~~tumors because there are no treatment groups, which are significantly different from controls, and because the maximum observed response is within the range of the historical control data (Table 5.3-1 in the Addendum). Obviously, ~~Care~~ care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[ADDIN EN.CITE
<EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</Rec
Num><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-
number><foreign-keys><key app="EN" db-
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timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government
Document">46</ref-
type><contributors><authors><author>OECD</author></authors><secondary-
authors><author>Environment, Health and Safety Publications</author></secondary-
authors></contributors><titles><title>Guidance Document 116 on the Conduct and
Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on
Testing and Assessment</tertiary-

title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>] and publications[ADDIN EN.CITE ADDIN EN.CITE.DATA] on the issue, the first choice should be the use of the concurrent controls (case-control studies). For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, it should be from the same timeframe for the exact strain, preferably from the same laboratory or the same supplier and preferably with the same pathologist[ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>]. This was not the case for the historical control database used by BfR. One of the mouse studies[ADDIN EN.CITE <EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[8]</DisplayText><record><rec-number>3421</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>] was clearly done before this historical control database was developed, one study[ADDIN EN.CITE <EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"

timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sugimoto</author></authors></contributors><titles><title>18-Month Oral Oncogenicity Study in Mice</title><secondary-title>Unpublished, designated ASB2012-11493 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ASB2012-11493 in BfR RAR</full-title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] used Crj:CD-1 mice rather than Crl:CD-1 mice, and 1 study[ADDIN EN.CITE <EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNum><DisplayText>[10]</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1385988909">611</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>JCFA</author></authors></contributors><titles><title>Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-location><publisher>Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization</publisher><isbn>WHO Technical Series #884</isbn><urls></urls></record></Cite></EndNote>] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2009</Year><RecNum>3970</RecNum><DisplayText>[16]</DisplayText><record><rec-number>3970</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446657481">3970</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Unknown</author></authors></contributors><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ABS2012-11492 in BfR RAR</full-title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] used the right strain, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[ADDIN EN.CITE <EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</RecNum><DisplayText>[21]</DisplayText><record><rec-number>3975</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446660626">3975</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford,

C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] was from studies in 7 laboratories using the Charles River Laboratory CD1 mice. Surprisingly, there is a second report[ADDIN EN.CITE <EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</RecNum><DisplayText>[22]</DisplayText><record><rec-number>3976</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446660642">3976</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford, C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[ADDIN EN.CITE <EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</RecNum><DisplayText>[21]</DisplayText><record><rec-number>3975</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446660626">3975</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford, C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows 5 and 4 studies out of 46 with adenomas and adenocarcinomas, respectively, ~~whereas~~ while the 2005 report[ADDIN EN.CITE <EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</RecNum><DisplayText>[22]</DisplayText><record><rec-number>3976</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446660642">3976</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford, C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year

Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows only ~~1~~ one study each out of 54 with a single adenoma and a single adenocarcinoma; all other studies had no tumors. Finally, in one mouse study[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2009</Year><RecNum>3970</RecNum><DisplayText>[16]</DisplayText><record><rec-number>3970</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446657481">3970</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Unknown</author></authors></contributors><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ABS2012-11492 in BfR RAR</full-title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] with malignant lymphomas, the comparison of the high exposure group to the control using four tests as reported by the BfR (Table 3-7) yielded p-values of 0.022, 0.022, 0.056 and 0.067; it is hard to see how this comparison to control can be easily disregarded.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that the evidence we were not allowed to see was overwhelmingly negative and that, since the studies we did review were not done under guideline principles, they should get less weight. No consideration is given to the different strains and cell lines studied in the literature when compared to the guideline studies; no consideration is given to the different endpoints provided in the literature data; and the human in-vivo evidence is completely ignored. ~~Because~~ Since we are not able to evaluate the single data that is proprietary, we are unable to comment on the veracity of their claim, but we would like ~~will note~~to inform that, ~~like~~ similar to~~the~~ animal carcinogenicity data, the evaluations (Tables 4.2.1 to 4.2.7) seem to be simple and possibly miss dose-response trends can occur.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but do not agree that this is strong support for an oxidative stress mechanism. They reduce the significance of these findings predominantly because of a lack of positive controls and because many of the studies used glyphosate formulations and not pure glyphosate. The WG disagrees with the BfR on this regard as well. We concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". Hence, based on the studies we reviewed, not only were we able

to identify glyphosate as inducing oxidative stress, but the formulations and AMPA as well.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A. In their 2013 Draft RAR, BfR concluded (Vol. 1, p. 139) "classification and labelling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential". How is this possible? Let's review the evidence and the conclusions.

The IARC WG saw an association between NHL and glyphosate in the human evidence, but could not rule out chance, bias and confounding; the IARC definition of "limited evidence"[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] for epidemiological data. BfR agreed, noting that other IARC categories are "not suitable". However the BfR concluded that an association was seen but dismissed it as insufficiently consistent.

The IARC WG ~~saw~~ identified significant effects for two tumors in two mouse studies and benign tumors in two rat studies. The BfR confirmed the statistically significant findings by the IARC WG, and agreed that the IARC ~~criteria of "sufficient" evidence in animals is~~criteria of "sufficient" evidence in animals are "fully met". BfR went on to identify two more mouse studies (bringing it to 3) with kidney tumors and another mouse study (bringing it to 2) with an increase in hemangiosarcoma, and two mouse studies showing increases in malignant lymphoma. Thus, all five mouse studies examined by the BfR were positive in at least 1 tumor site, 1 was positive in 3 tumor sites. Then using an 'inappropriate' historical control dataset in a potentially '~~n~~ inappropriate' way, dismiss all of these findings as a chance.

The IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available data. The BfR, while confirming the positive studies we ~~saw~~ identified for genotoxicity dismissed them because they were not guideline studies and because, in their interpretation, all of the guideline assays were negative. The BfR confirmed the positive studies we ~~saw~~ have

recognized for oxidative stress, noted some concern over these data, but concluded they could not use them, because there were no other data to support a finding of carcinogenicity or genotoxicity and the mechanism cannot stand alone.

The basis of the IARC evaluation was the "limited evidence" in humans and the "sufficient evidence" in animals, conclusions the BfR note are consistent with the IARC criteria, with supporting evidence of 2 strong mechanisms. Is glyphosate the agent causing this hazard? Given the human evidence (co-formulants only), the animal evidence (glyphosate only) and the mechanistic evidence (all forms), the most logical scientific conclusion is that glyphosate is the probable carcinogen. The BfR dismissed all evidence in humans, dismissed all evidence in animals and concluded there was one 'weak' mechanism that *'could not be used in isolation'*.

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We feel that the process used by the BfR to review human and animal evidence is fundamentally flawed and should be reconsidered. We are of the opinion that the scientific basis for rejecting the human, animal and mechanistic studies is, to the best of our knowledge, non-existent ~~and appears to have been designed to achieve a pre-determined goal rather than an objective scientific review~~ following a rigorous peer-review process. Finally, we strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide.

We stand by our conclusion that glyphosate is a probable human carcinogen.

[ADDIN EN.REFLIST]

Message

From: Martin, Matt [Martin.Matt@epa.gov]
Sent: 11/9/2015 6:26:19 PM
To: Egeghy, Peter [Egeghy.Peter@epa.gov]
Subject: RE: IARC Monograph vol 112- EFSA Review of Glyphosate

Yep.. I do not plan on being on this. I think we can site potential conflict of interest... or just generally conflicting...

~*
MATT MARTIN, PHD
RESEARCH BIOLOGIST | USEPA-ORD-NCCT
919-541-4104 | MARTIN.MATT@EPA.GOV
"IT'S TOUGH TO MAKE PREDICTIONS,
ESPECIALLY ABOUT THE FUTURE." - YOGI BERRA
~

-----Original Message-----
From: Egeghy, Peter
Sent: Monday, November 09, 2015 1:21 PM
To: Martin, Matt <Martin.Matt@epa.gov>
Subject: FW: IARC Monograph vol 112- EFSA Review of Glyphosate
Importance: High

Hi Matt,
I don't suppose that ORD management would be too keen on either of us singing this "response" letter.
What are your plans?
Thanks,
Peter

-----Original Message-----
From: Chris Portier [mailto Ex. 6 - Personal Privacy
Sent: Monday, November 09, 2015 6:05 AM
To: Isabelle Baldi <Isabelle.Baldi@isped.u-bordeaux2.fr>; Aaron Blair <blaira@exchange.nih.gov>; GMC24@columbia.edu; Egeghy, Peter <Egeghy.Peter@epa.gov>; Forastiere, Francesco <f.forastiere@deplazio.it>; Lin Fritschi <lin.fritschi@curtin.edu.au>; Jahnke, Gloria (NIH/NIEHS) [E] <jahnke@niehs.nih.gov>; Bill Jameson <drjameson@embarqmail.com>; Kromhout, J. (Hans) <h.kromhout@uu.nl>; frank lecurieux <frank.lecurieux@echa.europa.eu>; Martin, Matt <Martin.Matt@epa.gov>; John McLaughlin <John.McLaughlin@oahpp.ca>; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross <MRoss@cvm.msstate.edu>; Rusyn, Ivan <IRusyn@cvm.tamu.edu>; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea <A.Mannetje@massey.ac.nz>; Lauren Zeise <lxzeise@gmail.com>
Cc: Kate Guyton <GuytonK@iarc.fr>
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate
Importance: High

Dear all,

This week, the European Food Safety Agency (EFSA) will release their reassessment of glyphosate. In this review, they will conclude that glyphosate has no carcinogenic potential. This creates two problems as I see it. The first is that this wekens the strength of the IARC Monograph Program to stimulate change in how some of these agents are reviewed and addressed. The second is that it suggests we did not do our assessment adequately and that, had we seen all of the data they saw, we would have gotten a different answer. I do not intend to let this happen.

The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. This report was drafted prior to the IARC review. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. I have decided to draft a letter that I intend to try to get published in Carcinogenesis that addresses the points made by the BfR in their review. Failing my ability to get this into Carcinogenesis, EHP or some other Journal, I intend to send it as an open letter to the European Commission. I am enclosing both the BfR Addendum and my response for you to look over. I would like as many members of the Working Group to be co-authors on this as possible. If you wish to see changes made to the letter I can certainly work on that. If you are uncomfortable signing on to such a letter, I can appreciate that as in my previous job this would have been impossible. Please let me know by Friday November 13 if you can or cannot join me in this endeavor.

Sincerely,

Christopher Portier

Message

From: Chris Portier Ex. 6 - Personal Privacy
Sent: 11/10/2015 3:53:03 PM
To: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Aaron Blair [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy
CC: Kate Guyton [GuytonK@iarc.fr]
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate

Importance: High

Dear IARC V 112 Working Group Members,

I want to thank those of you who have gotten back to me with suggestions and a decision on whether to sign onto this letter. After much discussion with several colleagues, it seems best to me that rather than developing a letter from the WG, we develop a letter from many different scientists expressing concern about the differences between the BfR Addendum and the IARC WG report and questioning the scientific quality of the BfR Addendum. Thus, I have rewritten the document with many of your suggestions and with a tone that now reflects a letter from a group of concerned scientists. I will be sending this out shortly to a large list of folks, you included, to see if I can get sufficient buy-in to publish the letter. Thank you for your help up to this point.

C.

Message

From: Kromhout, J. (Hans) [h.kromhout@uu.nl]
Sent: 11/9/2015 3:35:31 PM
To: Chris Portier Ex. 6 - Personal Privacy Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Aaron Blair [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy
CC: Kate Guyton [GuytonK@iarc.fr]
Subject: RE: IARC Monograph vol 112- EFSA Review of Glyphosate

Hi Chris,

You did a great job and I'm more than willing to be a co-author of the letter.

Best, Hans

From: Chris Portier Ex. 6 - Personal Privacy
Sent: Monday, November 09, 2015 12:05 PM
To: Isabelle Baldi; Aaron Blair; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise
Cc: Kate Guyton
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate

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Sincerely,

Christopher Portier

Message

From: Chris Portier Ex. 6 - Personal Privacy
Sent: 11/9/2015 12:29:01 PM
To: Consolato Sergi Ex. 6 - Personal Privacy
CC: Kate Guyton [GuytonK@iarc.fr]; mross@cvm.msstate.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Teresa Rodriguez Ex. 6 - Personal Privacy frank lecurieux [frank.lecurieux@echa.europa.eu]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; John McLaughlin [John.McLaughlin@oahpp.ca]; Aaron Blair [blaira@exchange.nih.gov]; Lauren Zeise Ex. 6 - Personal Privacy Martin, Matt [Martin.Matt@epa.gov]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Bill Jameson [drjameson@embarqmail.com]; Mannetje, Andrea [A.Mannetje@massey.ac.nz]; GMC24@columbia.edu; Lin Fritschi [lin.fritschi@curtin.edu.au]; Forastiere, Francesco [f.forastiere@deplazio.it]
Subject: Re: IARC Monograph vol 112- EFSA Review of Glyphosate

Fantastic. Thanks.

On Nov 9, 2015, at 1:24 PM, Consolato Sergi Ex. 6 - Personal Privacy wrote:

Dear Chris,

Thank you for your email and your wise counteroffensive policy. I will sign the letter, but I would like to read the letter probably today and I will send you my comments by the end of the day.

Thank you again!

Best regards

Consolato

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From: Consolato Sergi Ex. 6 - Personal Privacy
Sent: 11/9/2015 12:24:53 PM
To: Chris Portier [Ex. 6 - Personal Privacy
CC: Kate Guyton [GuytonK@iarc.fr]; mross@cvm.msstate.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Teresa Rodriguez Ex. 6 - Personal Privacy frank lecurieux [frank.lecurieux@echa.europa.eu]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; John McLaughlin [John.McLaughlin@oahpp.ca]; Aaron Blair [blaira@exchange.nih.gov]; Lauren Zeise Ex. 6 - Personal Privacy Martin, Matt [Martin.Matt@epa.gov]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Bill Jameson [drjameson@embarqmail.com]; Mannetje, Andrea [A.Mannetje@massey.ac.nz]; GMC24@columbia.edu; Lin Fritschi [lin.fritschi@curtin.edu.au]; Forastiere, Francesco [f.forastiere@deplazio.it]
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From: Chris Portier Ex. 6 - Personal Privacy
Sent: 11/9/2015 11:05:19 AM
To: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Aaron Blair [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy
CC: Kate Guyton [GuytonK@iarc.fr]
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate
Attachments: IARCWG112ResponseV2.docx; BFRGlyphosateAddendum.pdf

Importance: High

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Sincerely,

Christopher Portier

Renewal Assessment Report

31.08.2015

Glyphosate
Addendum I to RAR

Assessment of
IARC Monographies
Volume 112 (2015):
Glyphosate

RMS: Germany

Version history (Addendum I)

Date	Reason for revision
31.08.2015	First Draft of Addendum I

Preface

In February 2015 a revised health risk assessment report on glyphosate prepared by the Federal Institute for Risk Assessment (BfR) was discussed at the expert meeting of the European Food Safety Authority (EFSA). Subsequently, the report was amended by the BfR. This revision comprised additional evaluation tables as well as additional amendments for more clarification on some factual matters. On 1 April 2015 BfR sent this supplemented and revised version of the report to the Federal Office of Consumer Protection and Food Safety (BVL) for forwarding to EFSA.

The International Agency for Cancer Research (IARC) of the World Health Organization (WHO) evaluated glyphosate as "probably carcinogenic to humans (Group 2A)", based on the available and evaluated studies by IARC. The full report on glyphosate from the IARC monograph (Volume 112) has been publicly available since 29 July 2015.

As Rapporteur Member State (RMS) for the European renewal of approval of glyphosate, Germany was commissioned by EFSA to evaluate the IARC Monographs Volume 112 on glyphosate by 31 August 2015, so that this scientific analysis could be included in the renewal process of the active substance glyphosate. Once this addendum has been subjected to a consultation process with the other Member States and a subsequent discussion in a separate Expert Meeting of EFSA at the end of September 2015, the results of this Addendum may be considered in the "EFSA Conclusion on the peer review of the pesticide risk assessment" of glyphosate.

Abstract

Based on the studies on cancer in humans IARC concluded: „*There is limited evidence in humans for the carcinogenicity of glyphosate*". The Rapporteur Member State (RMS) agrees with IARC that the other IARC categories are not suitable for the classification of the evidence from studies in humans. **The evaluation of the epidemiological studies by the RMS is comparable to IARC. However,** RMS adopts a more cautious view since **no consistent positive association was observed,** and the most powerful study showed no effect. The IARC interpretation is more precautionary. It was also noted that **in the epidemiological studies a differentiation between the effects of glyphosate and the co-formulants is not possible.**

Based on carcinogenicity studies in experimental animals IARC concluded that glyphosate induced a positive trend in the incidence of rare renal tumours; a positive trend for haemangiosarcoma in male mice and increased pancreatic islet-cell adenoma in male rats in two studies, and therefore: „*There is sufficient evidence in animals for the carcinogenicity of glyphosate*". A much larger number of animal studies have been performed to evaluate the carcinogenic potential of glyphosate than necessary by the legal requirements. In mice, a total of five long-term carcinogenicity studies using dietary administration of glyphosate were considered. In rats, seven chronic toxicity and carcinogenicity studies using dietary administration of glyphosate and two studies with application via drinking-water were reviewed.

- Renal tumours

  In two studies in CD-1 mice and one study in Swiss albino mice, the statistical analysis with the Cochran-Armitage test for linear trend yielded a significant result, whereas the analysis by pair-wise comparisons indicated no statistically significant differences between the groups and the incidences were within the historical control range of up to 6% for adenoma and carcinoma combined. A confounding effect of excessive toxicity cannot be excluded at the highest doses of 1460 - 4841 mg/kg bw/d. In both studies in CD-1 mice, but not in Swiss albino mice, the body weight gain was decreased by more than 15% compared to controls, but mortality/survival was not affected.

- Haemangiosarcoma:

  In two studies in CD-1 mice, the incidences of haemangiosarcoma in male mice were reconsidered for statistical evaluation. For both studies, the statistical analysis with the Cochran-Armitage test for linear trend yielded a significant result, whereas the analysis by pair-wise comparisons indicated no statistically significant differences between the groups. The background incidences for haemangiosarcoma in male CD-1 mice were up to 12% if multiple organs were considered. Therefore, the observed incidences for haemangiosarcoma were spontaneous and unrelated to treatment.

- Pancreatic and other tumours:

  The statistically significant increase in pancreatic tumours incidences in the male rats of the low dose groups are considered incidental. With regard to the positive trend for liver cell adenoma in male rats and thyroid C-cell adenoma in female rats for the study of Stout and Ruecker, IARC also noted a lack of evidence for progression.

- Malignant lymphoma:

  IARC also considered a review article containing information on five long-term bioassay feeding studies in mice, in which a statistically significant increase in the incidence of malignant lymphoma was reported, but the Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information. In three studies in CD-1 mice, the incidences of malignant lymphoma in male mice were reconsidered for statistical evaluation by the RMS. For two studies, the statistical analysis with the Cochran-Armitage trend test yielded a significant result, whereas the analysis by pair-wise comparisons indicated no statistically significant differences between the groups for all three studies. The incidences observed in the above studies, with a maximum of 12%, were all within the historical control range. Therefore, the observed malignant lymphomas were spontaneous and unrelated to treatment.

For an overall conclusion, the large volume of animal data for glyphosate has been evaluated using a weight of evidence approach. It should be avoided to base any conclusion only on the statistical significance of an increased tumour incidence identified in a single study without consideration of the biological significance of the finding. In summary, based on the data from five carcinogenicity studies in mice and seven chronic toxicity and carcinogenicity studies in rats, **the weight of evidence suggests that there is no carcinogenic risk related to the intended herbicidal uses and, in addition no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria.**

Based on the mechanistic and other studies, IARC concluded: „*There is mechanistic evidence for genotoxicity, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and cell proliferation or death of glyphosate*". Glyphosate has been tested in a broad spectrum of mutagenicity and genotoxicity tests *in vitro* and *in vivo*. **Taking into account all available data and using a weight of evidence approach, it is concluded that glyphosate does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria. In the absence of sufficient evidence for a carcinogenic risk related to the intended herbicidal uses the mechanistic and other studies do not provide further evidence for a carcinogenic mechanism.**

AMPA has been tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in an adequate range of assays. Taking into account all available data and using a weight of evidence approach, it is concluded that AMPA does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria.

Glyphosate-based formulations have been extensively tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in a wide range of assays. However, since formulation compositions are considered proprietary, the specific composition of the formulations tested was not available for the published studies. Positive results from *in vitro* chromosomal damage assays and tests for DNA strand breakage and SCE induction were reported in published studies. For specific glyphosate-based formulations, *in vivo* mammalian chromosomal aberration or micronucleus assays as well as tests for DNA adducts,

DNA strand breakage and SCE induction gave positive results in some published studies. However, no regulatory studies for these endpoints were provided. Thus, **for the different glyphosate-based formulations, no firm conclusions can be drawn with regard to a need for classification according to the CLP criteria.**

Considering the low level of metabolism and the chemical structure of glyphosate, glyphosate radical formation initiating oxidative stress appears unlikely. However, uncoupling or inhibition of mitochondrial oxidative phosphorylation also represents an established mechanism for ROS generation. Notably, uncoupling of oxidative phosphorylation by glyphosate has been reported in rat liver microsomes and a glyphosate formulation. Induction of oxidative stress can provide a mechanistic explanation for any observed cytotoxic/degenerative and indirectly genotoxic effects of substances. However, from the sole observation of oxidative stress and the existence of a plausible mechanism for induction of oxidative stress through uncoupling of mitochondrial oxidative phosphorylation alone, genotoxic or carcinogenic activity in humans cannot be deduced for glyphosate and glyphosate based formulations. Furthermore, the RMS concludes that the evidence from available data does not allow the conclusion that glyphosate caused immunosuppression. However it is to note that due to the small number of studies assessed and the fact that all studies show limitations, no robust information is available to conclude on the immunomodulatory action of glyphosate.

Glyphosate was included into the U.S. EPA Endocrine Disruptor Screening Program's (EDSP). It was concluded that, based on the Tier 1 assays that had been performed at different independent laboratories and taking into account the 'higher tier' regulatory safety studies, glyphosate should not be considered an endocrine disrupter or to have other receptor-mediated effects. Information on apoptosis and proliferation in cell systems from humans and mice was reported, but this was not considered as additional mechanistic evidence for carcinogenicity of glyphosate.

Results of four occupational and two para-occupational studies using various glyphosate-containing plant protection products have been evaluated in the International Agency for Cancer Research (IARC) monograph, which were carried out between 1988 and 2007 in different countries of North America and Europe. The recorded exposure values in these studies were below or in the same order of magnitude as those predicted in the Renewal Assessment Report (RAR). For resources on dietary exposure and for results on biological markers IARC refers to several selected reports from national food- and bio-monitoring programmes as well as to some studies in the public literature. With respect to exposure, no relevant deviating conclusions between the RAR and IARC were identified.

In addition, the RMS strongly recommends further genotoxicity studies in compliance with OECD test guidelines in general and for the representative formulation as confirmatory information for the authorisation of plant protection products.

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Annex 115

1 Exposure Data

1.1 Identification of the agent

The information reported in the sections 1.1.1 - 1.1.4 of the IARC Monographs Volume 112 (2015, ASB2015-8421) is generally summarized in line with the information in the cited references and with the information given in the RAR (2015, ASB2015-1194). Regarding section 1.1.4 it is noted that a different specification was derived by the RMS than by FAO (2000, ASB2015-8587). In summary, these sections appear to be an appropriate summary of the available knowledge on glyphosate.

1.2 Production and use

1.2.1 Production

1.2.1.1 Manufacturing process

In the IARC Monographs Volume 112 (2015, ASB2015-8421) it is stated that: "*To increase the solubility of technical-grade glyphosate acid in water, it is formulated as its isopropylamine, monoammonium, potassium, sodium, or trimesium salts*".

The manufacture and use of different active substance variants is not a glyphosate-specific feature; it is a common issue for many active substances. This circumstance has to be considered in the zonal/national authorisation procedure of the plant protection product. Thus, for the evaluation and assessment of the toxicological properties of active substance variants differently from the representative variant in the Annex I renewal, further studies may therefore be required for a bridging between the different variants of active substances on Member State level.

1.2.2 Uses

1.2.2.1 Agriculture

In the IARC Monographs Volume 112 (2015, ASB2015-8421) it is stated that: "*Common application methods include broadcast, aerial, spot and directed applications (EPA, 1993a).*" It should be noted that within the European Union, applications of plant protection products by aircraft are generally prohibited according to Directive 2009/128/EC (2009, ASB2015-8588). Only very few exceptions, for which it has to be applied particularly, can be granted, if no other effective method of pest control is available, e.g. for applications in the forest or on steep slopes in viticulture in Germany. However, no herbicidal applications by aircraft have ever been authorized. Thus, there is no aerial application of glyphosate-containing plant protection products, at least in Germany.

Within the scope of the European authorization procedure for glyphosate, only downwards directed applications have been intended and have been taken into account for risk assessment.

1.3 Measurement and analysis

Not one of the about 40 studies evaluated in Volume 3 sections B.5.2 - B.5.4 (2015, ASB2015-1194) are mentioned in the IARC Monographs Volume 112 (2015, ASB2015-8421). In section 1.3 of the IARC monograph in total 16 analytical reports from the open literature are cited. Two of them are

merely mentioned in the general introduction. Details of the remaining 14 studies are described in Table 1.1 of the IARC monograph. All details listed in Table 1.1 of the IARC monograph correspond exactly to the data of the cited studies. However, the limit of detection reported in these studies is estimated only and not statistically validated. A revised version of Table 1.1, listed in the Annex as Table A-5.5-1, additionally contains for that reason the limit of quantification, which is the only parameter that allows the evaluation of numerical data in other studies. In addition, Table A-5.5-1 contains the derivatisation agent (if used), a statement on the extent of validation data presented in cited studies and those sections of the IARC monograph, which refer to studies reported in section 1.3.

Due to the fact that quantitative analytical results will be more reliable if stable isotope labelled glyphosate is used as internal standard, it should be mentioned that the methods by [redacted] (2001, ASB2015-8239) and [redacted] (2013, ASB2015-7882) use such special internal standards.

Three of the studies reported in section 1.3 of the IARC monograph are cited in other sections. These are the studies by [redacted] (2004, ASB2012-11528), [redacted] (2011, ASB2015-7895) and Curwin et al. (2007, ASB2012-11597), which are mentioned in sections 1.4.1, 4.1.2, and 4.1.5. Due to missing analytical validation data in these studies, it is not possible to assess the reliability of results presented in these three studies. All other reports are not cited outside of section 1.3 of the IARC monograph.

In summary, the IARC Monographs Volume 112 (2015, ASB2015-8421) provides an overview on several studies published in scientific journals. About 50% of the methods reported in these studies are considered as sufficiently validated, even if the extent of validation data does not fully correspond to requirements of Regulation (EC) No 1107/2009 (2009, ASB2015-8589) as detailed in SANCO/825/00 rev. 8.1 (2010, ASB2015-8438).

1.4 Occurrence and exposure

1.4.1 Exposure

1.4.1.1 Occupational exposure

In section 1.4.1 of the IARC Monographs Volume 112 (2015, ASB2015-8421) results of four occupational and two para-occupational studies using various glyphosate-containing plant protection products are cited and summarized in Table 1.2. The studies were carried out between 1988 and 2007 in different countries of North America and Europe. Four of these studies ([redacted] 1988, ASB2015-7889; [redacted] 1992, TOX9650912; [redacted] 2005, ASB2012-11859, and [redacted] 2007, ASB2012-11597) have not yet been included in the RAR (2015, ASB2015-1194). Nevertheless, all six exposure studies have been roughly evaluated now (see Table A-5.5-2). A short summary of the evaluation of these studies is given in section 5.1.

1.4.1.2 Community exposure

For residues in food and feed references were made to several food monitoring reports and data from the EU, Denmark, United Kingdom and Brazil. The information are freely available, however, not included in the RAR due to the "safe-use" approach for the assessment of active substances under Regulation (EC) No 1107/2009 (2009, ASB2015-8589). The "safe-use" concept relies on supervised field trial data treated at the maximum application rates for the active substance, resulting in a more conservative exposure scenario compared to food monitoring results.

All studies reported by IARC on biological markers for glyphosate are also included in the RAR (2015, ASB2015-1194).

1.4.2 Exposure assessment

The methodology for the exposure assessment of glyphosate will be described in IARC Monographs Volume 112 for Malathion, which has not yet been published.

2 Studies of Cancer in Humans

In the section on cancer in humans (epidemiological studies) the IARC describes in Tables 2.1. and 2.2 the primary cohort and control studies with the reference, study location, study design, population size, exposure assessment methods, organ site, exposure category, exposed cases, risk estimate (95% confidence intervals) and covariates controlled and comments. Overall, these descriptions reflect the information in the articles (Instead of the cases and the response rates, it would have been helpful to detail the actual cases analysed.) The general discussion of the epidemiological studies was not available since it will appear in the IARC Monographs Volume 112 on Malathion which as of today has not been published. There are small differences in the way the strength of evidence may be judged and the limitations of the studies according to the descriptions in either report (RAR and IARC monograph). For example, the RMS considers it problematic that [redacted] (2002, ASB2012-11839) put two studies one on NHL and the other only on HCL together – different types of cancer without inclusion of the other respective cancer group – and analysed them together. Even though IARC does weighting and uses quality criteria it is not always detailed. It is not described in detail how the literature search and the selection of literature were done for the IARC report. Overall, BfR agrees that the relevant studies on NHL-lymphoma are included in the IARC monograph.

The epidemiological studies face several problems: only a small number of cancer cases are observed in all the individual studies, making it difficult to obtain clear results. Also the number of adequate epidemiological studies is limited. There are a lot of problems with confounders: in most studies glyphosate is analysed together with several other pesticides/insecticides so that the effects of each individual substance are difficult if not impossible to disentangle. Farmers who use one chemical substance may also use another. It is not clearly stated in which formulation glyphosate is used that is, it could be different brands with slightly different chemical mixtures and co-formulants, which may have carcinogenic effects. The exposure cannot be easily measured. For example no measures from biomarkers from the blood are used. Exposure is measured through interviews or questionnaires. Here, there is a big recall problem to judge the amount of exposure to the chemicals. Furthermore, there may be a recall biases since individuals with cancer are more likely to think about possible reasons for their cancer than healthy individuals. Moreover, in these studies we find a problem with the classification of the cancers. NHLs are not consistently defined over time. The definition has changed over time due to the use of different diagnostic methods: first morphological methods, than modern immunological methods were applied. Therefore, the NHLs reported do not always comprise the same cancers. For instance, some include, others exclude hairy cell leukaemia. Multiple myelomas may also be considered presently as NHL but not previously. Some studies are thus not comparable and some comparisons are difficult because of the in- and exclusion of certain subtypes which are not the same. This may bias the picture. The same applies to the combination in meta-analyses. IARC notes in quite a number of studies that there is limited power for glyphosate exposure. On the other hand, evidence from epidemiological studies has to be considered with all necessary care since at least uncertainties due to extrapolating from animal to human toxicology is avoided in this approach.

2.1 Cohort studies

12 publications have been reported by IARC in section 2.1. These publications are summarized in Table 2.1-1). The conclusion of most of these studies is that glyphosate did not cause different types of cancer or did not increase the risk of all cancers.

Glyphosate did not significantly increase the risk of prostate cancer, pancreatic cancer, melanoma, lung cancer, colon cancer, rectum cancer, kidney cancer, urinary bladder cancer, breast cancer, childhood cancer and all types of cancer. Cohort studies reported also no increased risk of all lymphohaematopoietic cancers, non-Hodgkin lymphoma (NHL), multiple myeloma, and of monoclonal gammopathy which is considered to be a premalignant disorder that often precedes multiple myeloma.

The results on NHL and multiple myeloma are discussed together with the results of case-control studies below (see section 2.2).

Table 2.1-1: Discussion of studies in section 2.1 Cohort studies of the IARC monograph

Study (Author/year)	Subject	Evaluation by IARC	Comment by RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 1996, ASB2015-7849	The Agricultural Health Study (AHS), large prospective cohort study	The only cohort study to date to have published findings on exposure and the risk of cancer at many different sites.	The data of this study were used in further studies. Conclusions are described there.	The AHS study was described in the RAR as basis for a number of publications.	Data of this publication were used for further studies. Conclusions on glyphosate are presented with these studies.
[redacted] 2003, ASB2012-11535	Use of pesticides and prostate cancer risk (based on AHS)	No significant exposure-response association of glyphosate with cancer of prostate was found.	Agreement	Yes, page 531	No significantly increased risk of prostate cancer.
[redacted] 2009, ASB2012-11544	Pesticide use and risk of pancreatic cancer (based on AHS)	The odds ratio for ever- versus never-exposure to glyphosate was 1.1 (0.6-1.7) while the odds ratio for the highest category of level of intensity-weighted lifetime days was 1.2 (0.6-2.6)	Agreement	Yes, Page 531	No significantly increased risk of pancreatic cancer.
[redacted] 2011, ASB2015-7868	Impact of pesticide exposure misclassification on estimates of relative risks in the AHS	Nondifferential exposure misclassification biases relative risk estimates towards the null in the AHS and tends to decrease the study power.	Glyphosate was not assessed in this study.	No, no assessment of glyphosate in this study	No assessment of glyphosate in this study
[redacted] 2010, ASB2015-8439	Pesticide use and risk of melanoma (based on data of AHS)	Exposure to glyphosate was not associated with cutaneous melanoma within the AHS.	Agreement	No	No increased risk of melanoma.
[redacted] 2005a, ASB2012-11605	Cancer incidence among glyphosate-exposed pesticide applicators (based on data of the AHS)	No increased risk of all cancers and of cancers in lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate and of melanoma, all lympho-haematopoietic cancers, NHL and leukaemia. For multiple myeloma the relative	Agreement with the reported results and the conclusion on limited power of the study. Further discussion of multiple	Yes, page 539	No increased risk of all cancers and of cancers in lung, oral cavity, colon, rectum, pancreas,

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		risk was 1.1 (0.5-2.4) when adjusted for age, but was 2.6 (0.7-9.4), when adjusted for multiple confounders. The study had limited power for the analysis of multiple myeloma. Missing data limit the interpretation of the findings.	myeloma in this study see also re-evaluation by [redacted] (2015, ASB2015-2284), below		kidney, bladder, prostate and of melanoma, all lympho-haematopoietic cancers, NHL and leukaemia. Interpretation of multiple myeloma is limited.
[redacted] 2005b, ASB2015-8437	Response in the discussion on the study of De Roos et al., 2005a, ASB2012-11605 (see above)	The study had limited power for the analysis of multiple myeloma. Missing data limit the interpretation of the findings.	Agreement	No, the paper is no study but only a response in the discussion on study of [redacted] 2005a, ASB2012-11605 (see above).	See [redacted] 2005a, ASB2012-11605
[redacted] 2005, ASB2012-11613	Pesticide use and breast cancer risk	No difference in incidence of breast cancer for women who reported ever applying glyphosate (odds ratio 0.9 (0.7-1.1); Women who never used glyphosate but whose husband had used (no information on duration of use): odds ratio 1.3 (0.8-1.9)	Agreement	Yes, page 531	No significantly increased risk of breast cancer.
[redacted] 2004, ASB2012-11620	Parental pesticide application and cancer risk in children; (based on data of AHS)	"For all the children of the pesticide applicators, risk was increased for all childhood cancers combined, for all lymphomas combined, and for Hodgkin lymphoma, compared with the general population." Limited power of the study for glyphosate exposure.	The cited IARC conclusion considers the risk for children of all pesticide applicators. However, this statement is not relevant for the assessment of glyphosate. There was an increased odds ratio in result of application of pesticides aldrin, dichlorvos and ethyl dipropylthiocarbamate. However, the results for glyphosate did not demonstrate any risk for childhood cancer. The odds ratios for maternal use and paternal use of glyphosate are	Yes, page 531	No increased risk of childhood cancer.

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			even clearly below 1. Agreement with the limited power of the study.		
[redacted] 2009, ASB2012-11875	Pesticide exposure and risk of monoclonal gammopathy (based on data of AHS)	No association between exposure to glyphosate and risk of monoclonal gammopathy of undetermined significance, a premalignant plasma disorder that often precedes multiple myeloma; odds ratio 0.5 (0.2-1.0)	The study authors conclude a nonsignificant decrease of monoclonal gammopathy of undetermined significance (MGUS), on the large data base of the AHS.	Yes, page 531	Nonsignificant decrease of risk of MGUS which usually precedes multiple myeloma
[redacted] 2007, ASB2015-8228	Pesticide use and risk of colorectal cancer (based on data of AHS)	Most of the 50 pesticides studied were not associated with risk of cancer of the colorectum, and the relative risks with exposure to glyphosate were 1.2 (0.9-1.6), 1.0 (0.7-1.5) and 1.6 (= 0.9-2.9) for cancers of the colorectum, colon and rectum respectively.	Agreement	No	No significantly increased risk of colorectal cancers.
[redacted] 2015, ASB2015-2284	Glyphosate and multiple myeloma, re-analysis of AHS data; data of the study of [redacted], 2005a, ASB2012-11605 (see above) are reanalysed	Sorahan confirmed that the excess risk of multiple myeloma was present only in the subset with no missing information.	The author concluded that "*this secondary analysis of AHS data does not support the hypothesis that glyphosate use is a risk factor for multiple myeloma*".	No, study was published after completion of the RAR.	No significantly increased risk of multiple myeloma based on the AHS data

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2.2 Case–control studies on non-Hodgkin lymphoma, multiple myeloma, and leukaemia

16 studies have been reported in section 2.2 of the IARC monograph and are summarized including comments of the RMS in Table 2.2-1.

Two of these 16 studies did not mention glyphosate ([redacted] 2001, ASB2015-8037 and [redacted] 1990, ASB2013-11501).

Five studies reported no increased risk of non-Hodgkin lymphoma and/or leukaemia or multiple myeloma. ([redacted] 1990, TOX2003-999; [redacted] 1992, ASB2015-7885; [redacted] 2012, ASB2012-11865; [redacted] 2004a, ASB2015-8238, and [redacted] 2009, ASB2012-11985).

Some of the reported studies had according to the IARC assessment in agreement with the RMS assessment a limited or even very limited power to assess effects of glyphosate. In three studies only 4 exposed cases have been compared with 2, 3 or 5 control subjects ([redacted] 2013, ASB2014-7523; [redacted] 1999, ASB2012-11838; and [redacted] 1998, TOX1999-687).

Further studies reported different, contradictory results. Depending from the used method of statistical analysis the risk was increased in some cases or not increased in other cases.

The relevant studies on non-Hodgkin lymphoma have been selected by [redacted] (2014, ASB2014-4819) to perform a meta-analysis. For the analysis of an association between glyphosate and non-Hodgkin lymphoma the following studies have been used: [redacted] 2003, ASB2012-11606; [redacted] 2005a, ASB2012-11605; [redacted] 2008, ASB2012-11614; [redacted] 2002, ASB2012-11839; [redacted] 2001, ASB2011-364, and [redacted] 2009, ASB2012-11985.

Furthermore, for the analysis of an association between glyphosate and B cell lymphoma 2 studies have been used: [redacted] 2008, ASB2012-11614 and [redacted] 2013, ASB2014-7523.

2 of the 6 studies used for the analysis of non-Hodgkin lymphoma reported no increased risk of non-Hodgkin lymphoma ([redacted] 2005a, ASB2012-11605 and [redacted] 2009, ASB2012-11985).

3 of the above cited 7 studies were considered by IARC to have limited or even very limited power ([redacted] 2002, ASB2012-11839 and [redacted] 2013, ASB2014-7523) or a low participation rate ([redacted] 2001, ASB2011-364).

Finally, IARC referred in a publication in Lancet ([redacted] 2015, ASB2015-7076) to 3 studies ([redacted] 2003, ASB2012-11606; [redacted] 2001, ASB2011-364, and [redacted] 2008, ASB2012-11614) in context with the conclusion that there was limited evidence in humans for carcinogenicity of glyphosate. These 3 studies are discussed by RMS in Table 2.2-2.

Table 2.2-1: Discussion of studies in section 2.2 Case-control studies on non-Hodgkin lymphoma (NHL), multiple myeloma and leukaemia of the IARC monograph

Study (Author/year)	Subject	Evaluation by IARC	Comment by RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 1990, TOX2003-999	Pesticide exposure and other agricultural risk for leukaemia	The odds ratio for glyphosate was 0.9 (0.5-1.6). The study had limited power to assess effects of glyphosate.	Agreement	No, because released before 2000	No increased risk of leukaemia, limited power of the study.
[redacted] 1993, TOX2002-1000	Pesticide exposure and multiple myeloma	The odds ratio for glyphosate was 1.7 (0.8-3.6). The study had limited power to assess effects of glyphosate.	Agreement	No, because released before 2000	Limited power of the study to assess effects of glyphosate.
[redacted] 1992, ASB2015-7885	Pesticides and other agricultural risk factors for non-Hodgkin lymphoma	The odds ratio for men who ever handled glyphosate was 1.1 (0.7-1.9), low power of the study to assess risk of NHL associated with glyphosate	Agreement	No, because released before 2000	No significantly increased risk of non-Hodgkin lymphoma, limited power of the study
[redacted] 2013, ASB2014-7523	Pesticide exposure and lymphoma risk	Odds ratio for glyphosate exposure was 3.1 (0.6-17.4); the study had a very limited power to assess the effects of glyphosate on risk of NHL	Agreement with the reported results and the conclusion on limited power of the study. Only 4 exposed cases and 2 control subjects have been considered in this study.	Yes, page 532	Very limited power of the study (only 4 exposed cases and 2 control subjects)
[redacted] 2003, ASB2012-11606	Pesticide exposure and risk of non-Hodgkin lymphoma	See separate assessment in this addendum	See separate assessment in this addendum	Yes, pages 529 and 537	See Table 2.2-2
[redacted] 2008, ASB2012-11614	Pesticide exposure and risk of non-Hodgkin lymphoma	See separate assessment in this addendum	See separate assessment in this addendum	Yes, pages 531 and 540	See Table 2.2-2
[redacted]	Pesticide exposure and risk of non-Hodgkin	The odds ratio for ever-use of glyphosate was 2.3 (0.4-13.4) in a univariate analysis, and 5.8	Agreement with the reported results and the conclusion on limited power	Yes, pages 530 and 534	no conclusion possible because of

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Study (Author/year)	Subject	Evaluation by IARC	Comment by RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
1999, ASB2012-11838	lymphoma	(0.6-54) in a multivariable analysis. The exposure frequency was low for glyphosate, and the study had limited power to detect an effect.	of the study. Only 4 exposed cases and 3 control subjects have been considered in this study.		limited power of the study (only 4 exposed cases and 3 control subjects)
[redacted] 2002, ASB2012-11839	Pesticide exposure and risk of non-Hodgkin lymphoma and hairy cell leukaemia	The study is a pooled analysis of two case-control studies (see [redacted] 1999, TOX1999-686, ASB2012-11838 and [redacted], 1998, TOX1999-687 in this addendum). Increased risk was found for glyphosate only in univariate analysis (odds ratio, 3.04 (1.08-8.52)), however, the odds ration decreased in multivariate analysis to 1.85 (0.55-6.20). The exposure frequency for glyphosate was low and the study had limited power.	Agreement with the presented results and the conclusion on limited power of the study. The study is a pooled analysis of two case-control studies (see separate discussion on studies of [redacted] 1999, TOX1999-686, ASB2012-11838 and [redacted], 1998, TOX1999-687 in this addendum).	Yes, page 530 and 535	See Table 2.2-2
[redacted] 2013, ASB2014-8030	Pesticide exposure and risk of multiple myeloma	The odds ratio for ever-use of glyphosate was 1.19 (0.76-1.87); no association was found for light users (≤ 2 days per year, odds ratio 0.72 (0.39-1.32), the odds ratio in heavier users (>2 days per year) was 2.04 (0.98-4.23). The study had relatively low response rates.	Agreement	Yes, page 532	No increased risk of multiple myeloma for ever use of glyphosate, higher (not significant) OR if mixing or applying glyphosate >2 days per year, low response rate
[redacted] et al., 2012, ASB2012-11865	Pesticide exposure and risk of non-Hodgkin lymphoma	Based on 38 cases exposed to glyphosate, the odds ratios were 1.14 (0.74-1.76) adjusted for age and province, and 0.99 (0.62-1.56) when additionally adjusted for medical history variables.	Agreement	Yes, page 531	No increased risk of non-Hodgkin lymphoma
[redacted] 2004a, ASB2015-	Pesticide exposure and risk of non-Hodgkin Lymphoma among	Subject with a history of asthma had a non-significantly lower risk of NHL than non-asthmatics. The odds ratio associated with	Agreement	No	No significantly increased risk of non-Hodgkin

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Study (Author/year)	Subject	Evaluation by IARC	Comment by RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
8238	asthmatics	glyphosate use was 1.4 (0.98-21.) among non-asthmatics and 1.2 (0.4-3.3) among asthmatics.			lymphoma for asthmatics and non-asthmatics; non-significantly lower risk of NHL for asthmatics than non-asthmatics
[redacted], 2001, ASB2011-364	Pesticide exposure and risk of non-Hodgkin lymphoma	Odds ratio of 1.26 (0.87-1.80) and 1.20 (0.83-1.74, adjusted for age, province, high-risk exposures) were observed for exposure to glyphosate. In an analysis by frequency of exposure to glyphosate, participants with 2+ days of exposure per year had an odds ratio of 2.12 (1.2-3.73) compared with those with some but ≤ 2 days of exposure. The study was large, but had relatively low participation rates.	See separate assessment in this addendum	Yes, pages 529 and 545	See Table 2.2-2
[redacted], 1998, TOX1999-687	Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia	An age-adjusted odds ratio of 3.1 (0.8-12) was observed for exposure of glyphosate. However, the study had limited power, only 4 exposed cases and there was no adjustment for other exposures.	Agreement with reported results and conclusions on limited power, only 4 exposed cases and 5 exposed controls are considered in this study	Yes, page 530	Limited power of the study (only 4 exposed cases and 5 exposed controls)
[redacted] 2009, ASB2012-11985	Pesticide exposure and risk of lymphoid neoplasms	The odds ratios associated with any exposure to glyphosate were 1.2 (0.6-2.1) for all lymphoid neoplasms, 1.0 (0.5-2.2) for NHL, 0.6 (0.2-2.1) for lymphoproliferative syndrome, 2.4 (0.8-7.3) for multiple myeloma, and 1.7 (0.6-5.0) for Hodgkin lymphoma.	Agreement with reported results. It should be considered in the discussion on an association between glyphosate and NHL that the OR of NHL in this study (12 exposed cases and 24 exposed controls) was 1.0.	No	See Table 2.2-2
[redacted] 2001, ASB2015-8037	Use of organophosphate pesticides and risk of non-Hodgkin lymphoma	IARC compared the numbers of cases and controls in this study with the study of De Roos et al., 2003; however, no information on glyphosate in this study	No information on glyphosate	No, no information on glyphosate	no information on glyphosate

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Study (Author/year)	Subject	Evaluation by IARC	Comment by RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 1990, ASB2013-11501	Exposure to 2,4-D and risk of non-Hodgkin Lymphoma	The study was mentioned by IARC because data were used in the study of [redacted] 2003	No information on glyphosate	No, no information on glyphosate	no information on glyphosate

Table 2.2-2: Summary of the RMS assessment on the strength of evidence and validity of epidemiological studies mentioned by IARC.

Short evaluation of the crucial studies in the draft of the Renewal Assessment Report (RAR) of the RMS	Main RMS comment after IARC publication on strength of evidence (none, low, medium, high) based on study type, internal and external validity and estimated effect size	Internal validity, such as quality aspects of the study, sample size, measurement biases, statistical uncertainty.	External validity & relevance for the RMS assessment: how close is the measured endpoint to the health endpoint of concern
[redacted] (2003, ASB2012-11606) had reported an association between NHL and glyphosate use.	No unequivocal evidence for causation of NHL by glyphosate based on a pooled analysis of three case control studies in the Midwestern United States (NHL diagnosed between 1979-1986) and reported exposures with 47 pesticides. Logistic regression and hierarchical model provide significant effect (OR, 2.1 with 95% confidence interval (CI) 1.1 to 4.0) and non-significant effect (OR, 1.6 with 95% CI 0.9 to 2.8), respectively, the latter with adjustment for multiple exposures and using prior probability of 0.3 for glyphosate as being carcinogenic. Contrary to common standards, the authors consider the result from the hierarchical model as significant. The description of the study design, analysis and results do not allow assessing methodological quality.	The internal validity cannot be assessed fully due to limitations in the reporting of the study. The past exposure status for a wide range of pesticides has been assessed in interviews, which is inherently prone to recall and interviewer bias. The study showed four out of 47 pesticides with lower limits of 95% confidence intervals greater than 1.0, indicative for a significant effect. The 47 pesticides may constitute multiple testing so that 5% of effects may show up by chance alone. The approximation of the relative risk using the OR is justified for NHL being a rare disease.	The relevance of the study for the current risk question is high. It is not known whether exclusion of females from the study population compromises the applicability of the findings to the general, European population.
[redacted] (2001, ASB2011-364) mentioned a non-significant positive association between self-reported glyphosate exposure and NHL in a Canadian study.	OR_{adj} = 1.20 (0.83/1.74): low effect size, not significant; no unequivocal evidence for causation of NHL by glyphosate. Well performed case control study on the male Canadian population from 6 provinces with one	Low/medium Multiplicity of pesticide exposure reported, but not the correlations. Tiered approach starting with pesticide classes, but no adjustment	Low/medium Should be considered for assessment as it is a well performed study exploring the endpoint NHL, which however is a collection of diseases.

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Short evaluation of the crucial studies in the draft of the Renewal Assessment Report (RAR) of the RMS	Main RMS comment after IARC publication on strength of evidence (none, low, medium, high) based on study type, internal and external validity and estimated effect size	Internal validity, such as quality aspects of the study, sample size, measurement biases, statistical uncertainty.	External validity & relevance for the RMS assessment: how close is the measured endpoint to the health endpoint of concern
	of four rare tumours (517 cases, 1506 controls). The study has some limitations typical of a case-control study (recall bias, misclassification of pesticide exposure) and without appropriate adjustment for multiple testing (multiple exposures and multiple endpoints).	for multiple testing (many pesticides, four tumours). While in this publication only NHL is considered, the study was planned and evaluated for four tumours.	The problem of multiple exposures is not easily overcome in reality; therefore it should not be over-stressed.
[redacted] (2008, ASB2012-11614) reported a case-control study which included 910 cases of NHL and 1016 controls living in Sweden. The highest risk was calculated for MCPA. Glyphosate exposure was reported by 29 cases and 18 controls, and the corresponding OR was 2.02.	OR = 2.02 (1.10-3.71) medium effect size, significant; a multivariate analysis gave no significant results. Case control study in 4/7 Swedish regions; all new cases during 29 months. 910 cases, 1016 controls from population registry. The study has some limitations typical of a case-control study (recall bias, misclassification of pesticide exposure) and without appropriate adjustment for multiple testing (multiple exposures).	Low/medium OR values and confidence intervals cannot be reproduced. The reported dependency from use intensity sounds logical but might as well be attributable to reporting bias.	Medium Study reported NHL diagnosis and subtypes according to WHO classification
[redacted] (2005, ASB2012-11605) make use of the AHS cohort.	OR = 1.1 [0.7, 1.9] for NHL, adjusted for age, demographic and lifestyle factors, and other pesticides.	High/medium In contrast to case-control-studies, a prospective cohort study does not suffer recall-bias. However, the problems of multiple exposures and multiple testing remain.	High/medium This study is the best we can hope for: A prospective cohort study with sensible stratification is optimal for establishing a causal relation. However, the problems of multiple exposures and of the possible effect of frequently used co-formulants remain.
[redacted] (2009, ASB2012-11985) did not find an association between NHL and glyphosate handling in a French case control study (OR = 1.0).	OR = 1.0 [0.5, 2.2] for any exposure (12 cases, 24 controls), OR = 1.0 [0.3, 2.7] for professional exposure (5 cases, 24 controls). The study has some limitations typical of a case-control study (recall bias, misclassification of pesticide exposure) and without appropriate adjustment for multiple testing (multiple exposures).	Medium Sensible stratification.	Medium Study reported NHL diagnosis and subtypes according to ICD-O-3 classification

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Short evaluation of the crucial studies in the draft of the Renewal Assessment Report (RAR) of the RMS	Main RMS comment after IARC publication on strength of evidence (none, low, medium, high) based on study type, internal and external validity and estimated effect size	Internal validity, such as quality aspects of the study, sample size, measurement biases, statistical uncertainty.	External validity & relevance for the RMS assessment: how close is the measured endpoint to the health endpoint of concern
[redacted] (2002, ASB2012-11839) This study pools data from [redacted] (1999, ASB2012-11838) with data from [redacted] (1998, TOX1999-687). Case-control study which included 515 male cases of NHL/ HCL and 1141 controls living in North and Middle Sweden. NHL and HCL diagnosed between 1987-1992), each case matched with two male controls, for age and country.	Univariate: OR = 3.04 (1.08 - 8.52) –medium effect size, only 8 exposed case and 8 exposed controls Multivariate: OR = 1.85 (0.55 - 6.2) with adjustment for study, study area, vital status, other pesticides Low effect size, Logistic regression model provide no significant effect.	Not reliable as the study combines two studies with different endpoints in order to increase the power. Note that it might have been justified to combine the endpoints in the first place (if it is true that HCL can be considered a subtype of NHL) but combining two weak studies in order to strengthen the result is technically invalid. The results in the multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate.	Not relevant for the link between glyphosate and NHL as the study reported NHL and HCL diagnosis. Limited power for glyphosate exposure.

HCL, Hairy cell leukaemia; NHL, non-Hodgkin lymphoma; OR, odds ratio

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The crucial studies used by IARC in the discussion on a relation between glyphosate exposure and risk of NHL were re-evaluated regarding strength of evidence and validity and there was no unequivocal evidence for a clear and strong association of NHL with glyphosate because of the limitations of these epidemiological studies such as being based on interviews with farmers or family members, the number of cases involved, and no knowledge of the actual amount of glyphosate or the type of glyphosate formula used. Even though the OR for an association between the exposure to glyphosate and NHL was slightly increased in all studies, it was not significant in the [redacted] (ASB2011-364), significant in the [redacted] (based on 29 cases) (ASB2012-11614) and not unequivocal in [redacted] (2003, ASB2012-11606) (a further study with data from the AHS in 2005 by [redacted] (ASB2012-11605) found no clear association between glyphosate and NHL, based on a large number of participating farmers), allowing no solid epidemiological statement on the basis of these three epidemiological studies. The studies need to be put in the context of the other epidemiological and experimental studies undertaken. Probably, further research needs to be carried out to study the usage and the impact of the formulation used in the field situation.

2.3 Case–control studies on other cancer sites

6 case control studies on other cancer sites were reported by IARC. The studies are summarized in Table 2.3-1.

One of these studies ([redacted], 2007, ASB2012-11909) did not separately assess glyphosate. The other 5 studies reported no increased risk or even a reduced risk of the investigated cancers (adenocarcinoma of stomach and oesophagus, gliomas and soft-tissue sarcoma).

Table 2.3-1: Discussion of studies in section 2.3 'Case-control studies on other cancer sites' and section 2.4 'Meta-analyses' of the IARC monograph

Study (Author/year)	Subject	Evaluation IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 2004b, ASB2012-11883	Pesticide use and risk of adenocarcinomas of stomach and oesophagus	For ever use of glyphosate, the odds ratio was 0.8 (0.4 - 1.4) for cancer of the stomach, and 0.7 (0.3 - 1.4) for oesophageal cancer; the power of the study was limited.	Agreement	Yes, page 531	No increased risk of adenocarcinomas of stomach and oesophagus
[redacted] 2004, ASB2015-8078	Pesticide exposure and risk of gliomas	No association was found with any of the pesticides assessed, including glyphosate. Glyphosate use was assessed, but specific results were not presented.	Agreement	No	No increased risk of gliomas
[redacted] 2005, ASB2012-11585	Pesticide exposure and risk of gliomas	There was a reduced risk for glyphosate (OR 0.7 (0.4 - 1.3).	Agreement	Yes, page 531	Reduced risk of gliomas
[redacted] 2005, ASB2012-11882	Pesticide use and risk of gliomas	There was a non-significant excess risk with glyphosate use for the overall group, but there was inconsistency between observations for self-responds and observations for proxy respondents. The study had limited power to detect an effect of glyphosate use and was difficult to interpret.	Agreement	Yes, page 530	Limited power of the study, difficult to interpret
[redacted] 2011, ASB2014-9625	Pesticide exposure and risk of soft-tissue sarcoma	The fully adjusted odds ratio for glyphosate was 0.90 (0.58 - 1.40).	Agreement	Yes, page 532	No increased risk of soft-tissue sarcoma
[redacted] 2007, ASB2012-11909	Pesticide exposure and risk of childhood leukaemia	Association of childhood cancer with glyphosate were reported only for an "other pesticides" category that also included other chemicals, glyphosate was not specifically assessed.	Agreement	Yes, page 530	No specific assessment of glyphosate

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Study (Author/year)	Subject	Evaluation IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 2014, ASB2014-4819	Meta-analysis, exposure to pesticides and non-Hodgkin lymphoma	The meta-analysis for glyphosate included six studies and yielded a meta-risk ratio of 1.5 (1.1 - 2.0). The working group noted that the most fully adjusted risk estimates from the articles by [redacted] (2002, ASB2012-11839) and [redacted] (2008, ASB2012-11614) were not used in this analysis. After considering the adjusted estimates of the two Swedish studies in the meta-analysis, the Working Group estimated a meta-risk-ratio of 1.3 (1.03 - 1.65).	Agreement, see separate assessment in this addendum (section 2.4).	Yes, page 531 and addendum	See separate assessment in this addendum (section 2.4).

OR, odds ratio

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2.4 Meta-analyses

Meta-analysis is an accepted investigation tool to provide a statistical summary across a number of studies with the same research question and similar setting. RMS has reviewed the study of [redacted] (2014, ASB2014-4819) as it is described in the IARC monograph and a meta-risk ratio of 1.3 (95% CI 1.03 - 1.65) I2=0%, P for heterogeneity 0.589) for NHL and glyphosate (glyphosate-based formulations, see discussion in section 2.5), as elicited by the IARC Working Group for glyphosate, could be reproduced by the RMS. The type of selection of the studies by IARC can be followed. This is a matter of definition and weighting the OR/RR from the case-control and cohort studies. The meta-risk ratio - the result of the meta-analysis - appears to show a moderate effect. The result is based on only 6 studies ([redacted] 2003, ASB2012-11606; [redacted] 2005, ASB2012-11605; [redacted] 2008, ASB2012-11614; [redacted] 2002, ASB2012-11839; [redacted] 2001, ASB2011-364; [redacted] 2009, ASB2012-11985), which qualified according to the set criteria. Although one of these ([redacted] 2005, ASB2012-11605) is a prospective cohort study, it was not ranked higher. And one study ([redacted] 2002, ASB2012-11839) was included in the meta-analysis even though its definition of NHL differs from the other studies. Even in the article, it is pointed out that further studies are needed.

The review of epidemiological studies on glyphosate and cancer by [redacted] (2012, ASB2014-9617) which was sponsored by Monsanto has not been discussed here as it is not mentioned in the IARC monograph. The authors conducted no meta-analysis, but list 7 cohort studies and 11 case-control studies; they found no evidence of consistent positive associations that would be indicative of a causal relationship between any site-specific cancer and exposure to glyphosate. Almost all of these studies were also reviewed by IARC and the RMS.

The conduct of systematic reviews and meta-analysis is considered primary research work and is typically not conducted by public agencies entrusted with assessing market authorisation studies.

2.5 Categorization of evidence from studies in humans

2.5.1 Contribution of co-formulants to the toxicity of glyphosate-based formulations

IARC concluded that the evidence relevant to carcinogenicity of glyphosate from studies in humans is classified into the category "*Limited evidence of carcinogenicity*".

IARC did not consider the differences of toxicity between the active substance glyphosate and of glyphosate-based formulations caused by the higher toxicity of co-formulants. The exposed cases in human studies are always exposed to glyphosate-based formulations and practically never to the active substance only.

All glyphosate-containing plant protection products contain surfactants or - if not present as an integral component - are to be mixed with surfactants as a compulsory additive to produce the ready-to-use dilution. As has already been discussed during the first Annex I inclusion procedure for glyphosate it became apparent that glyphosate-containing products were more toxic than glyphosate alone. This phenomenon was attributed to the presence of particular surfactants predominantly, namely the POE-tallowamines.

Already in the DAR on glyphosate (Germany, DAR, 1998, ASB2010-10302) that was prepared to support the first Annex I listing of the active substance, it was mentioned that surfactants could significantly contribute to the toxicity of glyphosate products.

Furthermore, a toxicological evaluation of tallowamine was prepared in 2010 and was included into the RAR (see pages 871-886 of the RAR (Volume 3 B.6), revised April 2015, ASB2015-1194).

With regard to nearly all toxicological endpoints under investigation, the POE-tallowamine was

clearly more toxic than glyphosate.

The higher toxicity of the surfactant might explain that also Roundup formulations when tested for different endpoints were more toxic than glyphosate ([redacted] 1982, TOX2002-693, and [redacted] 1983, TOX2002-694; [redacted] 2003, ASB2012-11600, and [redacted] 2007, ASB2012-2721).

Toxicological end points for which a higher toxicity of POE tallowamine in comparison to glyphosate was evidenced are summarized in Table 2.5-1.

Table 2.5-1: Comparison of toxicity data for glyphosate and the POE-tallowamine surfactant with CAS no. 61791-26-2 (from RAR, revised April 2015, ASB2015-1194).

End point	Glyphosate		POE-tallowamine surfactant	
Acute oral (rat)	LD_{50} > 5000 mg/kg bw		LD_{50}: 864 mg/kg bw	
Acute dermal (rabbit)	LD_{50} > 2000 mg/kg bw		LD_{50} >907 mg/kg bw	
Skin irritation	Not irritant		Irritant	
Eye irritation	Moderately to severely irritant		Severely irritant	
Skin sensitization	Negative		Sensitising	
DNA damage	Negative		Equivocal (some evidence at high and clearly toxic doses)	
	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)
Short-term toxicity (rat, oral, 90-day)	150	300	20	60
Short-term toxicity (dog, oral, approx. 3 month)	300	1000	21	42
Reproduction toxicity (rat)	700 (parental) 2000 (repro) 700 (offspring)	2000 (parental) >2000 (repro) 2000 (offspring)	38 (parental) 12 (repro) 12 (offspring)	74 (parental) 38 (repro) 38 (offspring)
Developmental studies (rat), maternal toxicity	300	1000	10.8	72
Developmental studies (rat), foetal effects	300	1000	72	216

Additionally to the above cited toxicological evaluation of tallowamine a large number of further, new studies demonstrated a higher toxicity of glyphosate-based formulations in comparison to the lower toxicity of the active substance glyphosate. Some of these studies are reported in the RAR (revised April 2015, ASB2015-1194) in chapter B.6.6.12 (in a comparison of the active substance glyphosate and glyphosate containing formulations concerning developmental and reproductive toxicity and endocrine disruption) and in chapter B.6.8.4 'Further published data released since 2000'.

Even in the new IARC monograph on glyphosate some studies have been reported which clearly demonstrate a higher toxicity of glyphosate-based formulations than of the active substance. ([redacted] 2009, ASB2009-7384; [redacted] 2005, ASB2009-9024; [redacted], 2007, ASB2009-9018, and [redacted] 2000, ASB2012-12046).

However, the evidence of a higher toxicity of glyphosate-based formulations caused by co-formulants was not noticed and not considered in the discussion by IARC.

Even though in some of the cited studies the authors clearly reported that a formulation was used, IARC discussed the effects only as glyphosate effects (e.g. IARC concluded in the study of [redacted] 2001, ASB2015-8279, "*A positive association between exposure to glyphosate and immunotoxicity in fish has been reported.*"). However, no active substance glyphosate was used in this study but a

formulation including co-formulants.

2.5.2 Conclusions on the classification of the evidence relevant to carcinogenicity from studies in humans into the IARC-categories

The categories of IARC as explained in the document IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Preamble, Lyon, 2006 explain the evaluation of epidemiological studies into certain categories (IARC, 2006, ASB2015-8291). On page 19 "Evaluation and rationale" it is stated: "*[...] It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.*"

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). In other words, the categories describe whether there may be a possible carcinogenic effect of the substance, but not the severity of this effect.

IARC notes for categories:

"*1. Evidence suggesting the lack of carcinogenicity: there are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure [...]*"

This is clearly not the case since the studies are not mutually consistent in not showing a positive association, instead results are inconsistent: a considerable number show no positive correlation, others may indicate a positive association. IARC states further "*Bias and confounding should be ruled out with reasonable confidence [...]*". This is not the case for the epidemiological studies with glyphosate, since in most studies several chemicals are studied (and used) and the substance under consideration has been used in various mixtures with different co-formulants. Furthermore, a problem with estimating the exposure based on several studies using questionnaires and interviews should be considered since these instruments are prone to recall biases. The studies are not showing consistently a positive association. Most studies do not show an association, but some do. However, it is difficult to demonstrate or prove the lack of carcinogenicity using an epidemiological study. Therefore, RMS agrees that glyphosate cannot be classified in category 1.

"*2. Inadequate evidence of carcinogenicity: the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absences of a causal association between exposure and cancer, or no data on cancer in humans are available*" (as defined by IARC). IARC does not classify glyphosate in this category, since there were limited data available, even though a lot of the studies have low statistical power, when assessing them individually, due to the number of individuals involved. The AHS cohort-study does list a considerable number of participants. Furthermore, the epidemiological studies show serious limitations because of recall bias, mixture of several chemicals, and missing knowledge about the exact products used (formulations) and low sample sizes, etc. The adherence of each primary study to pertinent guidelines for epidemiological studies was not re-assessed by RMS.

Despite limitations of all involved individual primary studies, it would seem inadequate to neglect the body of evidence they can provide in combination. RMS agrees with IARC that glyphosate should not be classified in this category as the description does not fit the available data even though some of them are weak.

In the 3rd category: "*Limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence*". This in other words means a trend in some studies is observed, however, no clear causal relationship can be established and no consistent positive association and the result can be an artefact due to chance or confounding. The IARC classifies the epidemiological evidence of glyphosate in this category. However, the authors of the meta-analysis ([redacted] 2014,

ASB2014-4819) recommend for all pesticides further studies. The result could also be described as: most studies show no association, but a few studies do and in the most recent meta-analysis a weak trend between glyphosate NHL and a subgroup B cell lymphoma was observed. Therefore, an effect cannot be ruled out. Following the logic of the classification system of IARC, the RMS can accept this interpretation since the categories 1 and 2 do not appear to be correct, neither is the last category 4 with "sufficient evidence of carcinogenicity". It is a matter of expressing the remaining uncertainty in classifying glyphosate, since a lot of studies show no effect of glyphosate but some do with a weak carcinogenic potency as expressed through the odds ratios. It should be noted that the estimated OR of 1.3 by the IARC based on the meta-analysis of [redacted] 2014, ASB2014-4819, indicates a rather weak association and that epidemiological associations cannot be interpreted as proof of causality. It is noteworthy that the most powerful study, the AHS, the prospective cohort-study, which in epidemiological terms is best suited to study the relationship, showed no association with cancer incidence overall or with most of the cancer subtypes, only a suggested association with multiple myeloma incidence was found, which needs to be followed up ([redacted] 2005, ASB2012-11605). Therefore, the evaluation of the RMS has a slightly different nuance than the evaluation of IARC, as the RMS is more cautious in describing the evidence for a positive relationship, even though the evaluation of the individual studies is similar.

The RMS sees a particular problem with the co-formulants of glyphosate-based formulations. As described in chapter 2.5.1 for the surfactants and thus for the glyphosate-based formulation a higher toxicity may be observed than for the glyphosate on its own. In the epidemiological studies it is not possible to differentiate between glyphosate itself and the other co-formulants, as well as different formulations used.

3 Cancer in Experimental Animals

In its Monograph Volume 112 IARC came to the conclusion, that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015, ASB2015-8421). In contrast and based on animal studies evaluated by the RMS Germany, the RMS had come to the conclusion that classification and labelling for carcinogenicity is not considered appropriate (RAR, April 2015, ASB2015-1194).

Potential explanations for the differences in the outcome of the evaluation may be that:

i) a different database was used by both agencies and/or

ii) the data provided by the study reports was evaluated differently, and/or

iii) the overall database was interpreted differently, e.g. as the result of different decision criteria.

Subsequently, all of these potential explanations are discussed.

i) Differences in the data basis

The database used by IARC and/or RMS for evaluation of neoplastic effects of glyphosate in laboratory animals is presented in the Table 3-1 (mice) and Table 3-2 (rats) below.

Overall, IARC evaluated three mouse and seven rat studies. Additionally IARC reported three further mouse studies and three more rat studies, which were however, not evaluated because these studies were not available in sufficient detail to the IARC Working Group.

Overall, RMS evaluated six mouse and ten rat studies. In addition to all studies assessed by IARC, RMS also evaluated the studies mentioned by IARC that were not fully assessed by the IARC Working Group. Hence, the data-basis considered by both agencies is essentially similar with three more mouse and three more rat studies fully evaluated by the RMS.

Table 3-1 and Table 3-2 summarize the studies reported by IARC and/or RMS, providing references and study owners, study type, duration, routes of exposure, dose levels, results (with respect to carcinogenicity) and the respective evaluations by both agencies.

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Table 3-1: Animal studies in mice reported by IARC and/or RMS.

Reference, study ID, Lot, purity, owner	Study type duration route dose levels	Results (with respect to carcinogenicity)	Evaluation by IARC	Evaluation by RMS	Comments
[redacted] 1983, TOX9552381, Lots NB 1782608/3 and 1782610/7, 99.7%, [redacted]	Carcinogenicity, 2 year, CD-1, feeding 0, 1000, 5000, 30000 ppm (equal to 157/190; 814/955; 4841/5874 mg/kg bw/d in m/f)	*Males:* Renal tubule adenoma: 0/49, 0/49, 1/50 (2%), 3/50 (6%) [P for trend = 0.016] *Females:* No data provided on the kidney Report from the PWG of the EPA (1986): *Males:* Renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%) [NS] Renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%) [P = 0.037; Cochran–Armitage trend test] Renal tubule adenoma or carcinoma (combined): 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%) [P = 0.034; Cochran–Armitage trend test]	Positive trend for renal tubule adenoma and carcinoma in male mice	No significant increase in tumour incidence observed in any groups of treated animals	Different statistical approaches reported by RMS and IARC. Due to differences in statistical evaluation RMS did not consider the renal tubule tumours as significant
[redacted] 1993, TOX9552382, Lot 206-JaK-25-1, 98.6%, [redacted]	Carcinogenicity, 2 year, CD-1, feeding 0, 100, 300, 1000 mg/kg bw/d (dietary levels regularly adjusted)	*Males*: Haemangiosarcoma: 0/50, 0/50, 0/50, 4/50 (8%) [P < 0.001, Cochran-Armitage] Histiocytic sarcoma in the lymphoreticular/ haemopoietic tissue: 0/50, 2/50 (4%), 0/50, 2/50 (4%) [NS] *Females:* Haemangiosarcoma: 0/50, 2/50 (4%), 0/50, 1/50 (2%) [NS] Histiocytic sarcoma in the lymphoreticular/ haemopoietic tissue: 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%) [NS]	Positive trend for haem-angiosarcoma in males	No significant increase in tumour incidence observed in any groups of treated animals	Different statistical approaches reported by RMS and IARC. Due to differences in statistical evaluation RMS did not consider the haemangiosarcomas as significant

Reference, study ID, Lot, purity, owner	Study type duration route dose levels	Results (with respect to carcinogenicity)	Evaluation by IARC	Evaluation by RMS	Comments
[redacted] 2009, ASB2012-11492, Lot H05H016A, 95.7%, [redacted]	Carcinogenicity, 18 month, CD-1 (ICR), feeding 0, 500, 1500, 5000 ppm (equal to 71/98; 234/299; 810/1081 mg/kg bw/d in m/f)	No relevant carcinogenic response reported	Study reported but not evaluated	No significant increase in tumour incidence observed in any groups of treated animals	Study not considered by IARC
[redacted] 2001, ASB2012-11491, Lot 01/06/97, >95.14%, [redacted]	Carcinogenicity, 18 month, Swiss albino, feeding 0, 100, 1000, 10000 ppm (15; 151; 1460 mg/kg bw/d, sexes combined since values were similar)	Higher incidence of malignant lymphoma at top dose level in males and females (significant according to Cochran-Armitage and Peto test)	Study reported but not evaluated	Considering historical control range and consistency, some evidence for carcinogenicity but not sufficient for classification	Study not considered by IARC
[redacted] 1997, ASB2012-11493, T-941209, 97.56% and T-950308, 94.61%, [redacted]	Carcinogenicity, 18 month, CD-1 (ICR), feeding 0, 1600, 8000, 40000 ppm (165/153; 838/787; 4348/4116 mg/kg bw/d in m/f)	No relevant carcinogenic response reported	Study reported but not evaluated	No significant increase in tumour incidence observed in any groups of treated animals	Study not considered by IARC
[redacted] 2010, ASB2012-11829, glyphosate based formulation (glyphosate, 41%; POEA, ~15%) (referred to as "glyphosate") dissolved in 50% ethanol; DMBA dissolved in 50% ethanol, and TPA dissolved in 50% acetone, Published study	Initiation–promotion study; Skin only 20 M/group Group I: untreated control Group II: glyphosate only: 25 mg/kg bw topically, 3 × /week, for 32 weeks Group III: single topical application of DMBA, 52 µg/mouse, followed 1 week later by TPA, 5 µg/mouse, 3 × /week, for	Skin tumours Group I: 0/20 Group II: 0/20 Group III: 20/20*, 7.8 ± 1.1 *P < 0.05 vs groups VI and VII Group V: 0/20 Group VI: 0/20 Group VII: 0/20 Group VIII: 8/20*, 2.8 ± 0.9 *P < 0.05 vs group VI	Inadequate study for the evaluation of glyphosate carcinogenicity	Inadequate study for the evaluation of glyphosate carcinogenicity	Both evaluations agree

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Reference, study ID, Lot, purity, owner	Study type duration route dose levels	Results (with respect to carcinogenicity)	Evaluation by IARC	Evaluation by RMS	Comments
	32 weeks Group IV: single topical application of glyphosate, 25 mg/kg bw, followed 1 week later by TPA, 5 µg/mouse, 3 × /week, for 32 weeks Group V: 3 × /week topical application of glyphosate, 25 mg/kg bw, for 3 weeks, followed 1 week later by TPA, 5 µg/mouse, 3 × /week, for 32 weeks Group VI: single topical application of DMBA, 52 µg/mouse Group VII: topical application of TPA, 5 µg/mouse, 3 × /week, for 32 weeks Group VIII: single topical application of DMBA, 52 µg/mouse, followed 1 week later by topical treatment with glyphosate, 25 mg/kg bw, 3 × /week, for 32 weeks				

Table 3-2: Animal studies in rats reported by IARC and RMS.

Reference, study id, Lot, purity, owner	Study type duration route dose levels	Results	Evaluation by IARC	Evaluation by RMS	Comments
[redacted] 1993, TOX9750499,	Combined chronic toxicity/carcinogenicity; 2 year;	No relevant carcinogenic response reported	No significant increase in tumour incidence observed	No significant increase in tumour	Both evaluations agree

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Reference, study id, Lot, purity, owner	Study type duration route dose levels	Results	Evaluation by IARC	Evaluation by RMS	Comments
229-JaK-5-1, 98.9% and 229-JaK-142-6, 98.7%, [redacted]	Sprague-Dawley; feeding		in any groups of treated animals	incidence observed in any groups of treated animals	
[redacted] 1996, TOX9651587, 2 batches used, 96.8/96.0%, [redacted]	Combined chronic toxicity/carcinogenicity; 2 year; Wistar; feeding 0, 100, 1000, 10000 ppm (6.3/8.6, 59.4/88.5, 595.2/886 mg/kg bw/d in m/f)	No relevant carcinogenic response reported	Study reported but not evaluated	No significant increase in tumour incidence observed in any groups of treated animals	No evaluation by IARC
[redacted] 1990, TOX9300244; XLH-264, 96.5%, [redacted]	Combined chronic toxicity/carcinogenicity; 2 year; Sprague-Dawley; feeding 0, 2000, 8000, 20000 ppm (89/113, 362/457, 940/1183 mg/kg bw/d in m/f)	*Males:* Pancreas (islet cell): Adenoma: 1/43 (2%), 8/45 (18%; P = 0.018), 5/49 (10%), 7/48 (15%; P = 0.042) Carcinoma: 1/43 (2%), 0/45 (0%), 0/49 (0%), 0/48 (0%) Adenoma or carcinoma (combined): 2/43 (5%), 8/45 (18%), 5/49 (10%), 7/48 (15%) Liver: Hepatocellular adenoma: 2/44 (5%; P for trend = 0.016), 2/45 (4%), 3/49 (6%), 7/48 (15%) Hepatocellular carcinoma: 3/44 (7%); 2/45 (4%), 1/49 (2%), 2/48 (4%) Hepatocellular adenoma or carcinoma (combined): 5/44 (11%), 4/45 (9%), 4/49 (8%), 9/48 (19%) *Females:* Pancreas (islet cell): Adenoma: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Carcinoma: 0/60, 0/60, 0/60, 0/59 Adenoma or carcino-ma (combined): 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Thyroid: C-cell	Pancreas: There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma but a significant increase in adenoma in males in two dose levels Liver: Significant positive trend for hepatocellular adenoma in males, no progression to malignancy Thyroid: Significant positive trend for C-cell adenoma in females	No significant increase in tumour incidence observed in any groups of treated animals	Due to differences in statistical evaluation RMS did neither consider the pancreatic islet cell tumours nor the hepatocellular adenomas nor the thyroid c-cell adenomas for classification

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Reference, study id, Lot, purity, owner	Study type duration route dose levels	Results	Evaluation by IARC	Evaluation by RMS	Comments
		adenoma: 2/60 (3%), 2/60 (3%), 6/60 (10%), 6/60 (10%)			
[redacted] 1981, TOX2000-595 and TOX2000-1997, XHJ-64, 98.7%, [redacted]	Combined chronic toxicity/carcinogenicity; 26 months; Sprague-Dawley; feeding 0, 3/3.4, 10.3/11.2, 31.5/34 mg/kg bw/d in m/f (dietary levels adjusted according to values as measured in the 1st week)	*Males:* Pancreas (islet cell): Adenoma: 0/50 (0%), 5/49* (10%), 2/50 (4%), 2/50 (4%) Carcinoma: 0/50 (0%), 0/49 (0%), 0/50 (0%), 1/50 (2%) Adenoma or carcinoma (combined): 0/50 (0%), 5/49 (10%), 2/50 (4%), 3/50 (6%) *Females:* Pancreas (islet cell): Adenoma: 2/50 (4%), 1/50 (2%), 1/50 (2%), 0/50 (0%) Carcinoma: 0/50 (0%), 1/50 (2%), 1/50 (2%), 1/50 (2%) Adenoma or carcinoma (combined): 2/50 (10%), 2/50 (2%), 2/50 (74%), 1/50 (2%)	There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma, but a significant increase in one of the treated groups of males	No significant dose dependent increase in tumour incidence observed in any groups of treated animals	Both evaluations basically agree; they disagree in the interpretation of the significant increase of pancreatic islet cell adenoma at the lowest dose group in males
[redacted] 2009, ASB2012-11490, H05H016A, 95,7%, [redacted]	Combined chronic toxicity/carcinogenicity; 2 year; Wistar; feeding Combined chronic toxicity/carcinogenicity; 2 year; Wistar; feeding	No relevant carcinogenic response reported	Study reported but not evaluated	No significant dose dependent increase in tumour incidence observed in any groups of treated animals	No evaluation by IARC
[redacted] 2001*, ASB2012-11488, P30, 97.6%, [redacted]	0, 2000, 6000, 20000 ppm (121/145, 361/437, 1214/1498 mg/kg bw/d in m/f)	No relevant carcinogenic response reported	No significant increase in tumour incidence observed in any groups of treated animals	No significant increase in tumour incidence observed in any groups of treated animals	Both evaluations agree
[redacted] 1997, ASB2012-11484, ASB2012-11485, ASB2012-11486, ASB2012-11487,	Combined chronic toxicity/carcinogenicity; 2 year; Sprague-Dawley; feeding 0, 3000, 10000, 30000 ppm (104/115, 354/393, 1127/1247 mg/kg bw/d	No relevant carcinogenic response reported	Study reported but not evaluated	No significant increase in tumour incidence observed in any groups of treated animals	No evaluation by IARC

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Reference, study id, Lot, purity, owner	Study type duration route dose levels	Results	Evaluation by IARC	Evaluation by RMS	Comments
T-941209, 97.56% and T-950308, 94.61%, [redacted]	in m/f)				
[redacted] TOX2000-1998, P24, 95.6%, [redacted]	Chronic toxicity; Wistar-derived; 12 months; feeding 0, 2000, 8000, 20000 ppm (141/167, 560/671, 1409/1664 mg/kg bw/d in m/f)	No relevant carcinogenic response reported	No significant increase in tumour incidence observed in any groups of treated animals	No significant increase in tumour incidence observed in any groups of treated animals	Both evaluations agree
[redacted] 2012, (re-published 2014) ASB2012-15514, Published study	24-month study (10 males and 10 females per group) Sprague Dawley Drinking water at 0, 5 x 10^{-5} mg/L, 400 mg/L and 2.25 g/L of total glyphosate from a glyphosate based formulation	*Males:* No significant increase in tumour incidence observed in any of the treated groups *Females:* Mammary tumours (mainly fibroadenomas and adenocarcinomas): 5/10 (50%), 9/10 (90%), 10/10 (100%)*, 9/10 (90%) Pituitary lesions (hypertrophy, hyperplasia, and adenoma): 6/10 (60%), 8/10 (80%), 7/10 (70%), 7/10 (70%)	Inadequate study for the evaluation of glyphosate carcinogenicity	Inadequate study for the evaluation of glyphosate carcinogenicity	Both evaluations agree
[redacted] 2000, ASB2013-9829, Published study	24 month-study Wistar drinking water containing 0, 300, 900 or 2700 mg/L, 55 m/f per group	No relevant carcinogenic response reported	No significant increase in tumour incidence observed in any groups of treated animals	No significant increase in tumour incidence observed in any groups of treated animals	Both evaluations agree

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Summary of results by IARC:

Critical results with respect to carcinogenicity identified by IARC included the occurrence of renal tubular adenoma and carcinoma in CD-1 mice in one study ([redacted] 1983, TOX9552381), the occurrence of haemangiosarcoma in male mice in one other study ([redacted] 1993, TOX9552382) and the occurrence of pancreatic islet cell tumours and hepatocellular adenomas in rats ([redacted] 1990, TOX9300244).

IARC summarized: "*[...] there was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carcinoma is a rare tumour in this strain of mice. No significant increase in tumour incidence was seen in female mice in this study. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. No significant increase in tumour incidence was seen in female mice in this study. For the five feeding studies in rats, two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males - one of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site. One study in Wistar rats was inadequate for the evaluation because of the short duration of exposure. In the study in Wistar rats given drinking-water containing glyphosate, there was no significant increase in tumour incidence. A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation-promotion study in male Swiss mice. The study of a glyphosate-based formulation in drinking-water in Sprague-Dawley rats was inadequate for the evaluation because of the small number of animals per group, and the limited information provided on tumour histopathology and incidence in individual animals. These studies of a chemical mixture containing glyphosate were considered inadequate to evaluate the carcinogenicity of glyphosate alone.*" (IARC, 2015, ASB2015-8421)

In addition, IARC reported but did not evaluate the studies by [redacted] (1997, ASB2012-11493) in CD-1 mice, [redacted] (2001, ASB2012-11491) in Swiss albino mice and [redacted] (2009, ASB2012-11490) in CD-1 mice.

Summary results by RMS:

As apparent from the Tables above, RMS had not considered any of the tumours listed by IARC as potentially relevant for classification due to a lack of statistical significance and limited consistency between the studies. Critical results in terms of carcinogenicity identified by the RMS included the occurrence of malignant lymphoma in Swiss mice. RMS argued, however, that the murine tumours are not to be considered for classification because of the high background level of these tumours in Swiss mice.

In summary, RMS stated: "*Taking all this information together, a treatment-related effect in the study by [redacted] (2001, ASB2012-11491) in Swiss albino mice cannot be completely excluded. However, the weak increase in malignant lymphoma even over the historical control of the performing laboratory was clearly confined to this single study and strain since it was not reproducible in four other valid long-term studies. Thus, there is only very limited evidence of a carcinogenic potential of glyphosate as a high-dose phenomenon in mice of a susceptible strain. Most likely, perhaps, age-related neoplastic changes might be exacerbated by long-lasting administration of high doses. Swiss albino mice with high background prevalence of malignant lymphoma could be more vulnerable than other strains.*

Since the more frequent occurrence of malignant lymphoma was confined to a very high dose level that was administered over a long period, glyphosate was considered unlikely to pose a carcinogenic risk in humans. Classification and labelling for carcinogenicity is not considered appropriate by the RMS because of the following considerations:

(1) *The presumed effect was observed statistically significant in only one of five long-term studies in mice in a strain with a rather high background incidence of malignant lymphoma. Evidence*

coming from two other studies one more study is even more equivocal because a certain increase there did not gain statistical significance. In a third study, a (non-significant) increase in top dose incidence was explained and contravened by historical control data. Taking into account the huge amount of information on historical control incidences, there was no evidence of a similar effect in any other study.

(2) Although the increase in lymphoma incidence in the study by [redacted] (2001, ASB2012-11491) was statistically significant in both sexes, it was still within the (small) historical control range of the performing laboratory for females. No evidence of a similar effect in female mice was obtained in any other study.

(3) No evidence of carcinogenicity was obtained in a total of six valid 2-year studies in rats (see above) in which sufficiently high dose levels were employed.

(4) The dose with a significantly higher lymphoma incidence (1460 mg/kg bw/day) is more than 2900 times higher than the proposed ADI and the margin to the expected consumer exposure is even wider." (RAR, April 2015, ASB2015-1194)

ii) Differences in evaluation of individual study reports

Due to the application of different statistical approaches selected for evaluation, IARC and RMS came to diverging conclusions when evaluating cancer incidences in animal studies. IARC included a trend test (generally according to Cochran-Armitage) for statistical evaluation of the data (IARC, 2015, ASB2015-8421). In contrast, initially, the RMS relied on the statistical evaluation provided with the study reports, which was performed and documented as foreseen in the individual study plans (RAR, April 2015, ASB2015-1194). The later were mostly based on pairwise comparison of treatment groups using tests including Fishers exact test, Chi-Square test, or Z-test. As a consequence, IARC reported a positive carcinogenic response in some of these studies, while RMS did not. According to guidance documents for the evaluation of carcinogenicity studies published in support of respective OECD test guidelines (OECD 2012, ENV/JM/MONO(2011)47, ASB2015-8445 and OECD 2002, ENV/JM/MONO(2002)19, ASB2013-3754), both statistical approaches are appropriate.

In order to systematically assess the impact of choice of statistical method, a number of neoplastic endpoints in key-studies were re-evaluated by the RMS for this Addendum using the Fishers exact test and the Cochran-Armitage test, as both are explicitly recommended in the OECD guidance documents cited above. The Cochran-Armitage Test was performed using BMDS version 2.4.0.70. The Fisher-Yates test (Fisher's exact test) was done using SigmaPlot version 11.2.0.5. The Fisher exact test was replaced by the Chi-square test if N was >50 for all groups.

(a) Renal adenoma and carcinoma in male mice:

The positive trend for renal adenoma and carcinoma in the study by [redacted] (1983, TOX9552381) as reported in the IARC evaluation could be confirmed (Table 3-3). When the trend test was also applied to the incidences of renal tubular tumours as reported by [redacted] (1997, ASB2012-11493), another positive result was obtained (Table 3-4). The IARC working group did report but not evaluate this study. In both cases, the pairwise comparison of treatment groups using the Fishers exact test did not show statistically significant differences (Table 3-3 and Table 3-4).

Table 3-3: **Renal adenoma and carcinoma in male CD-1 mice ([redacted] 1983, TOX9552381), originally reported data and re-evaluation by pathology working group (PWG). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each endpoint a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose		**report**	**Re-evaluation by PWG**		
(mg/kg bw)	N	adenoma	adenoma	carcinoma	combined
0	49	0	1	0	1
157	49	0 (1.000)	0 (1.000)	0 (1.000)	0 (1.000)
814	50	1 (1.000)	0 (0.495)	1 (1.000)	1 (1.000)
4841	50	3 (0.242)	1 (1.000)	2 (0.495)	3 (0.617)
Trend test (p-value)		0.0080	0.2473	0.0370	0.0339

Table 3-4: **Renal tubular tumors adenoma in CD-1 mice ([redacted] 1997, ASB2012-11493). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. A Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	**male**	
(mg/kg bw)	N	adenoma
0	50	0
165	50	0 (1.000)
838	50	0 (1.000)
4348	50	2 (0.495)
Trend test (p-value)		0.0078

b) Haemangiosarcoma in male mice:

The statistically positive trend test for haemangiosarcoma in the study by [redacted] (1993, TOX9552382) as reported by IARC could be confirmed. Direct comparison of the incidences in males of the high dose and the control group using the Fishers exact test resulted in a p-value of 0.059 just above the significance level of 0.05 (Table 3-5). In addition, there was a positive trend for haemangiosarcoma when the data from [redacted] (1997, ASB2012-11493) was included in the re-evaluation.

Table 3-5: **Haemangiosarcoma in male CD-1 mice ([redacted] 1993, TOX9552382; [redacted] 1997, ASB2012-11493). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. A Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose		Haemangiosarcoma	Dose	Haemangiosarcoma
(mg/kg bw)	N	[redacted] (1993, TOX9552382)	(mg/kg bw)	[redacted] (1997, ASB2012-11493)
0	50	0	0	0
100	50	0 (1.000)	165	0 (1.000)
300	50	0 (1.000)	838	0 (1.000)
1000	50	4 (0.059)	4348	2 (0.495)
Trend test (p-value)		0.0004		0.0078

c) Malignant lymphoma in mice:

IARC and RMS reported a significantly increased incidence of malignant lymphoma in males of the high dose group in the study of [redacted] (2001, ASB2012-11491) compared to the concurrent control. Interestingly, when the analysis was performed using the Fischers exact test rather than the Z-test as done by the authors of the study report, a p-value of 0.077 > 0.05 instead of 0.002 < 0.01 was obtained. The trend test (not reported by IARC) also provided a p-value above the significance level of 0.05 (Table 3-6).

However, re-evaluation of the incidences if malignant lymphoma reported by [redacted] (2009, ASB2012-11490) and [redacted] (1997, ASB2012-11493) showed statistically significant increases with dose for male CD-1 mice (Table 3-7 and Table 3-8). Re-analysis of malignant lymphoma data reported by of [redacted] (1993, TOX9552382) confirmed the earlier evaluation, showing no treatment-related increases in incidence (Table 3-9).

Table 3-6: **Malignant Lymphoma in Swiss albino mice ([redacted] 2001, ASB2012-11491). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each sex, a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	male		female	
(mg/kg bw)	N	Malignant Lymphoma	N	Malignant lymphoma
0	50	10	50	18
15	50	15 (0.356)	50	20 (0.837)
151	50	16 (0.254)	50	19 (1.000)
1460	50	19 (0.077)*	50	25 (0.225)*
Trend test (p-value)		0.0655		0.068

* The original study report indicated a statistically significant increase (p<0.05).

Table 3-7: **Malignant Lymphoma in CD-1 mice ([redacted] 2009, ASB2012-11490). Chi square test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each sex, a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	male		female	
(mg/kg bw)	N	Malignant Lymphoma	N	Malignant lymphoma
0	51	0	51	11
71	51	1 (1.000)	51	8 (0.611)
234	51	2 (0.475)	51	10 (1.000)
810	51	5 (0.067)*	51	11 (1.000)
Trend test (p-value)		0.0037		0.3590

* Chi –square test was chosen in accordance to the recommendations of the statistics package used. Using the Fishers exact test, a p-value of 0.056 (two-sided) is calculated. Depending on the tool used for calculation, the two-tailed Z-test produced p-values of 0.0220, 0.0219 and 0.067.

Table 3-8: **Malignant Lymphoma in CD-1 mice ([redacted] 1997, ASB2012-11493). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each sex, a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	male		female	
(mg/kg bw)	N	Malignant Lymphoma	N	Malignant lymphoma
0	50	2	50	6
165	50	2 (1.000)	50	4 (0.741)
838	50	0 (0.495)	50	8 (0.774)
4348	50	6 (0.269)	50	7 (1.000)
Trend test (p-value)		0.0085		0.2971

Table 3-9: **Malignant Lymphoma in CD-1 mice ([redacted] 1993, TOX9552382). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each sex, a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	male		female	
(mg/kg bw/d)	N	Malignant Lymphoma	N	Malignant lymphoma
0	50	4	50	14
100	50	2 (0.678)	50	12 (0.657)
300	50	1 (0.362)	50	9 (0.342)
1000	50	6 (0.741)	50	13 (1.000)
Trend test (p-value)		0.0760		0.4831

d) Pancreatic islet cell adenoma in rats:

IARC noted that based to the tumour incidences reported by [redacted] (1990, TOX9300244), there was a significant increase in pancreatic adenoma in males in two dose levels but no statistically significant positive trend nor a progression to carcinoma. In contrast, RMS did not report any statistically significant effect for pancreatic tumours in this study. When re-evaluating the reported incidences using Cochran-Armitage trend testing and Fishers exact test, absence of a statistically positive trend was confirmed and a significant difference to the incidence in the control group was found for the low dose group only (Table 3-10). The latter result is in agreement with the study summary provided in the revised RAR Volume 3 (April 2015, ASB2015-1194).

Table 3-10: **Pancreatic islet cell tumors in SD rats ([redacted] 1990, TOX9300244). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. A Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	**male**	
(mg/kg bw)	N	adenoma
0	43	1
89	45	8 (0.030)
362	49	5 (0.209)
940	48	7 (0.062)
Trend test (p-value)		0.1687

In addition, IARC reported for the study of [redacted] (1981, TOX2000-595, TOX2000-1997) in SD rats a significant increase in the incidence of pancreatic tumours in one of the treated groups of males in the absence of statistically significant positive trends over all dose groups and no indication for progression to carcinoma. The RMS did not report significant pancreatic tumour findings for this study. Re-evaluation confirmed a significantly increase number of adenomas and combined adenomas + carcinomas for the male low dose group when compared to the concurrent controls. In addition, a significantly positive trend for carcinomas in male animals was found that has not been previously reported. There were no significant findings for pancreatic tumours in the females (Table 3-11 and Table 3-12).

Table 3-11: **Pancreatic tumors in male SD rats ([redacted] 1981, TOX2000-595, TOX2000-1997). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each endpoint a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	**male**			
(mg/kg bw)	N	adenoma	carcinoma	adenoma + carcinoma
0	50	0	0	0
3	49	5 (0.027)	0 (1.000)	5 (0.027)
10.3	50	2 (0.495)	0 (1.000)	2 (0.495)
31.5	50	2 (0.495)	1 (1.000)	3 (0.242)
Trend test		0.5284	0.0496	0.3207

Dose	male			
(p-value)				

Table 3-12: **Pancreatic tumors in female SD rats ([redacted] 1981, TOX2000-595, TOX2000-1997). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each endpoint a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	female			
(mg/kg bw)	N	adenoma	carcinoma	adenoma + carcinoma
0	50	2	0	2
3.4	50	1 (1.000)	1 (1.000)	2 (1.000)
11.2	50	1 (1.000)	1 (1.000)	2 (1.000)
34	50	0 (0.495)	1 (1.000)	1 (1.000)
Trend test (p-value)		0.9025	0.2969	0.7371

e) Hepatocellular adenoma and carcinoma in rats:

IARC reported a significantly positive trend for hepatocellular adenoma in males in the study of [redacted] (1990, TOX9300244) without indications for progression to malignancy. In contrast, RMS did not report any statistically significant effect for liver tumours in this study. When re-evaluating the reported incidences using Cochran-Armitage trend testing and Fishers exact test, the statistically positive trend was confirmed for adenomas and no positive trend was observed for adenoma and carcinoma combined. In accordance with evaluations by IARC and RMS, a significant difference to the incidence in the control group was not found for the respective treatment groups (Table 3-13).

Table 3-13: **Liver cell tumors in SD rats ([redacted] 1990, TOX9300244). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. For each endpoint a Cochran-Armitage trend test was performed, with p-values reported in a separate row.**

Dose	male	liver	
(mg/kg bw)	N	adenoma	adenoma + carcinoma
0	44	2	5
89	45	2 (1.000)	4 (0.739)
362	49	3 (1.000)	4 (0.732)
940	48	7 (0.162)	9 (0.392)
Trend test (p-value)		0.0171	0.0752

f) Thyroid C-cell adenoma in rats:

The IARC Working Group reported a significant positive trend for C-cell adenoma in females of the study of Stout and Ruecker (1990, TOX9300244). The RMS did not report any statistically significant effect with respect to thyroid tumours for this study. The statistically significant positive trend could be confirmed using the Cochran-Armitage test (Table 3-14).

Table 3-14: Thyroid C-cell adenoma tumors in female SD rats ([redacted] 1990, TOX9300244). Fishers exact test was used to compare each treatment group to the respective control group, with p-values reported in brackets. A Cochran-Armitage trend test was performed, with p-values reported in a separate row.

Dose	**female**	**Thyroid**
(mg/kg bw)	N	C-cell adenoma
0	60	2
113	60	2 (1.000)
457	60	6 (0.167)
1183	60	6 (0.167)
Trend test (p-value)		0.0435

iii) Differences in decision criteria

In addition to the statistical significance, the RMS had taken into account consistency of results as a criterion for evaluation. Since no consistent significant increase in any of the tumour types was originally reported in the available studies the apparent effects were not considered sufficient for classification in the RAR (April 2015, ASB2015-1194).

As for the database, a part of the criteria used by both agencies is essentially similar while some deviations exist in terms of classification.

The IARC has used their own published criteria for evaluation of carcinogenic effects (IARC, 2006, ASB2015-8291) while RMS is generally bound to the classification criteria laid down in EU Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures (in brief referred to as CLP-criteria) (2008, ASB2015-8591).

Criteria IARC:

When considering the level of evidence for a carcinogenic effect, both sets of criteria are similar.

The IARC and CLP criteria state, that:

"*Sufficient evidence of carcinogenicity*: [The Working Group considers that] a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

"Limited evidence of carcinogenicity": The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs." (IARC 2006, ASB2015-8291; Reg (EC) No 1272/2008, Annex 1, 3.6.2, ASB2015-8591).

Conclusion by IARC:

Based on these criteria it is obvious that IARC concludes on "sufficient evidence of carcinogenicity" in experimental animals, because the above criteria for this conclusion are fully met.

Additional Criteria CLP:

The CLP criteria are taking into account the IARC criteria. However, the CLP regulation also states that when evaluating carcinogenic effects, additional criteria have to be taken into account. In Annex I to Reg (EC) 1272/2008 it is summarized:

"*Annex I: 3.6.2.2.4.* Additional considerations (as part of the weight of evidence approach Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

Annex I: 3.6.2.2.5. The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

Annex I: 3.6.2.2.6. Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) tumour type and background incidence;

(b) multi-site responses;

(c) progression of lesions to malignancy;

(d) reduced tumour latency;

(e) whether responses are in single or both sexes;

(f) whether responses are in a single species or several species;

(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;

(h) routes of exposure;

(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(j) the possibility of a confounding effect of excessive toxicity at test doses;

(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity." (Reg (EC) No 1272/2008, Annex 1, ASB2015-8591)

Conclusion RMS:

Considering these additional criteria when taking into account the rat studies RMS argued that:

"No evidence of carcinogenicity was obtained in any of these studies." and when considering the majority of mouse studies RMS argues (possibly referring to point (a) and (j)) that: "*Again, there was no evidence of carcinogenicity of glyphosate in any of the studies.*"

Accordingly for the malignant lymphoma previously observed in one mouse study only, RMS argues, referring to point (a) of the aforementioned list: *"Taking all this information together, a treatment-related effect in the study by* [redacted] *(2001, ASB2012-11491) in Swiss albino mice cannot be completely excluded. However, the weak increase in malignant lymphoma even over the historical control of the performing laboratory was clearly confined to this single study and strain since it was not reproducible in four other valid long-term studies. Thus, there is only very limited evidence of a carcinogenic potential of glyphosate as a high-dose phenomenon in mice of a susceptible strain. Most likely, perhaps, age-related neoplastic changes might be exacerbated by long-lasting administration of high doses. Swiss albino mice with high background prevalence of malignant lymphoma could be more vulnerable than other strains.*

Since the more frequent occurrence of malignant lymphoma was confined to a very high dose level that was administered over a long period, glyphosate was considered unlikely to pose a carcinogenic risk in humans [...]" (RAR , April 2015, ASB2015-1194).

Overall, based on the study results and the CLP criteria RMS concluded that the evidence of carcinogenicity is conclusive but not sufficient for classification.

Summary and conclusion:

The statistical analysis by IARC was confirmed and extended. Based on the data evaluated by the respective agencies and the different criteria used for concluding on a potential carcinogenic effect, it is evident that both agencies have come to reasoned conclusions. The OECD test guideline on the evaluation of carcinogenicity studies states: "*Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.*" (OECD 2002, 2012, ASB2013-3754, ASB2015-8445). Accordingly, renal tumours in male CD-1 mice would be considered as treatment-related based on positive trend tests in two studies ([redacted] 1983, TOX9552381, [redacted] 1997, ASB2012-11493). Malignant lymphoma in males could be considered treatment related in the study by [redacted] (2001, ASB2012-11491) using Swiss albino mice based on the original positive Z-test for the high dose males and the studies of [redacted] (2009, ASB2012-11490) and [redacted] (1997, ASB2012-11493) in CD-1 mice based on positive trend tests for males.

4 Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Introduction

The introduction in the IARC monograph is in line with the conclusions from the RAR (April 2015, ASB2015-1194). However, in the RAR a broader database was used to assess the microbial metabolism in the gut, suggesting a lower relevance as concluded by IARC.

4.1.2 Absorption

The data presented in the IARC monograph is also nearly completely reported in the RAR (April 2015, ASB2015-1194). The only additional study in the IARC monograph is an *in vitro* model by [redacted] (2005, ASB2012-12043), describing an increased paracellular permeability due to glyphosate at >10 mg/mL.

4.1.3 Distribution

In general the conclusion for the distribution of glyphosate is comparable between the IARC monograph and the RAR (April 2015, ASB2015-1194), suggesting short half-live times between 10 to 33 h. Also, tissue levels were identified to be highest in kidney.

Two studies presented in the IARC monograph were not reported in the RAR ([redacted] 2008, ASB2012-12059 and [redacted] 2010, ASB2015-7858), however their results do not lead to different conclusions for the distribution of glyphosate.

4.1.4 Metabolism and modulation of metabolic enzymes

Both the IARC monograph and the RAR (April 2015, ASB2015-1194) concluded that glyphosate metabolized to a very small amount into AMPA in mammals. The IARC monograph relied on two studies not included in the RAR ([redacted] 2008, ASB2015-8160 and [redacted] 2010, ASB2015-7858). However in total the RAR provided a broader database for this endpoint. Concerning the modulation of metabolic enzymes all studies used by IARC were also presented in the RAR. No deviating conclusions were drawn in both documents.

4.1.5 Excretion

Except for one study on glyphosate and AMPA levels in urine of a rural population in Colombia ([redacted] 2009, ASB2015-8039), which is in line with results from other studies, all references presented by IARC were also cited in the RAR. Also the conclusion that systemically absorbed glyphosate is not metabolized efficiently and is mainly excreted unchanged into the urine is identical. No discrepancies between the RAR (April 2015, ASB2015-1194) and the IARC monograph were identified.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Glyphosate has been studied for genotoxic potential in a wide variety of assays. The studies which were evaluated by IARC were carried out in exposed humans, in human cells *in vitro*, in other mammals *in vivo* and *in vitro*, and in non-mammalian systems *in vivo* and *in vitro*, respectively, are summarized in Tables 4.1-4.5 of the IARC monograph.

The IARC Working Group has reviewed only reports that have been published or accepted for publication in the openly available scientific literature as well as data from government agency reports that are publicly available.

In contrast, the RMS which undertakes the task of evaluating an active substance according to Regulation (EC) No 1107/2009 (2009, ASB2015-8589) shall review the complete dossier (that contains the full text of the individual test and study reports) and the scientific peer-reviewed open literature on the active substance and its relevant metabolites.

Thus, the RMS has assessed the relevant published data on genotoxicity of glyphosate which has also been reviewed by IARC, and additionally a number of regulatory studies which were not available to IARC, but a great many of them were evaluated in the review article of [redacted] (2013, ASB2014-9587). The regulatory studies were mostly generated in compliance with internationally agreed test guidelines, which include principles for conducting studies, reporting results, and analysing and interpreting data.

For regulatory purposes, test methods preferred for use are (ECHA, 2015: Guidance on information requirements and chemical safety assessment; Chapter R.7a: Endpoint specific guidance; Version 4.0, ASB2015-8657):

In vitro test methods: OECD 471, OECD 476, OECD 476, OECD 473, OECD 487.

In vivo test methods, somatic cells: OECD 475, OECD 474, OECD 488, OECD 486, OECD 489.

In vivo test methods, germ cells: OECD 483, OECD 478, OECD 488.

To be able to evaluate the mutagenic potential of a substance in a comprehensive way, information is required on its capability to induce gene mutations, structural chromosome aberrations (clastogenicity) and numerical chromosome aberrations (aneugenicity).

Classification of substances for (germ cell) mutagenicity according to CLP criteria:

Hazard classification for germ cell mutagenicity primarily aims to identify substances causing heritable mutations or being suspected of causing heritable mutations. A secondary aim is that the hazard class germ cell mutagenicity offers supporting information with respect to the classification of carcinogenic substances. This is expressed by the broad meaning of the hazard statements 'H340: May cause genetic defects' and 'H341: Suspected of causing genetic defects' which comprises heritable genetic damage as well as somatic cell mutagenicity. Thus, classification as a germ cell mutagen (Category 1A, 1B, and 2) classifies for the hazard heritable genetic damage as well as providing an indication that the substance could be carcinogenic.

Classification as a Category 1A mutagen:

Epidemiological studies have been to date unable to provide evidence to classify a substance as a Category 1A mutagen. Hereditary diseases in humans for the most part have an unknown origin and show a varying distribution in different populations. Due to the random distribution of mutations in the genome it is not expected that one particular substance would induce one specific genetic disorder. Therefore, it is unlikely that such evidence may be obtained by epidemiological studies to enable for classification of a substance as a Category 1A mutagen.

Classification as a Category 1B mutagen:

Classification in Category 1B may be based on positive results of at least one valid *in vivo* mammalian germ cell mutagenicity test. In case there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

If there are only positive results of at least one valid *in vivo* mammalian somatic mutagenicity test but no respective data on mammalian germ cells are available, additional evidence is required to be able to classify as mutagen in Category 1B. Such additional data must prove that the substance or its metabolite(s) interacts *in vivo* with the genetic material of germ cells. It is also possible to obtain supporting evidence in an *in vivo* genotoxicity test with mammalian germ cells. In addition, genetic damage to germ cells in exposed humans proven to be caused by substance exposure may offer respective information. In case of other supporting evidence or where there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

Classification as a Category 2 mutagen:

Classification in Category 2 may be based on positive results of a least one *in vivo* valid mammalian somatic cell mutagenicity test, indicating mutagenic effects in somatic cells. A Category 2 mutagen classification may also be based on positive results of a least one *in vivo* valid mammalian somatic cell genotoxicity test, supported by positive *in vitro* mutagenicity results. Genetic damage to somatic cells in exposed humans shown to be caused by substance exposure supported by positive *in vitro* mutagenicity results may also offer respective information warranting classification as a Category 2 mutagen. *In vitro* results can only lead to a Category 2 mutagen classification in a case where there is support by chemical structure activity relationship to known germ cell mutagens. In the case where there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

Principles for the evaluation of published studies used by the RMS

For the analysis of published studies, the RMS made generally a comparison to the criteria in guidelines used for regulatory purposes. However, these criteria do not represent an absolute judgment standard but can provide a way for evaluating the quality of the protocols used in various published studies. [redacted] (2013, ASB2014-9587) have summarized a number of relevant issues to be considered: "*Some of the criteria are rarely met in scientific publications and should be given little or no weight in evaluating the studies. For example, data for individual cultures and individual animals are not commonly included in publications in scientific journals. These data are presumably collected but are usually summarized as group means with a measure of variance for the treatment and control groups. This is not considered to be a significant omission in a scientific publication. However, other guideline features are more essential as scientific quality standards and should be considered as having greater weight in evaluating a study. For example, there are consistent recommendations that assays involving visual scoring (e.g. chromosomal aberration, micronucleus and sister chromatid exchange (SCE) endpoints) should use slides that are independently coded so that scoring is performed without any knowledge of the treatment or practice and studies that do not explicitly include a description of coding or "blind" scoring in the methodology would appear to have a deficiency either in the methodology, or perhaps a limitation in the description of the methodology used if coding was actually used and either not indicated or was assumed to be indicated by a reference citation. Other examples of guideline features that have clear experimental scientific value are the use of concurrent negative and positive controls and concurrent measurement and reporting of toxicity endpoints in main experiments, especially in in vitro mammalian cell assays.*"

Glyphosate:

Assessment and conclusion of IARC:

According to the conclusion of IARC, there is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells *in vitro* (IARC monograph, Table 4.2), in mammalian model systems *in vivo* (IARC monograph, Table 4.3) and *in*

vitro (IARC monograph, Table 4.4), and studies in other non-mammalian systems *in vivo* (IARC monograph, Table 4.5) and *in vitro* (IARC monograph, Table 4.6). *In vivo* studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow. The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage. Tests in bacterial assays gave consistently negative results (IARC monograph, Table 4.6).

Assessment and conclusion of the RMS:

In vitro studies:

1. Bacterial assays gave consistently negative results.
2. *In vitro* mammalian cell gene mutation tests gave consistently negative results.
3. *In vitro* mammalian chromosome aberration tests and *in vitro* micronucleus tests: several regulatory studies conducted according to internationally agreed test guidelines which gave negative results at concentrations up to 1250 µg/ml (Table 4.2-1). In contrast, induction of chromosomal aberrations in bovine lymphocytes was reported in one non-guideline study without metabolic activation at concentrations of 3-30 µg/mL ([redacted] 1998, ASB2013-9836), and induction of micronucleus formation in CHO cells was reported in one non-guideline study with metabolic activation at concentrations of 5-100 µg/mL ([redacted] 2014, ASB2014-8086).
4. Further *in vitro* tests (indicator tests): Positive results for induction of sister chromatid exchange (SCE) were reported in cultured human and bovine lymphocytes without metabolic activation in two published non-guideline studies (Table 4.2-2).

   Positive results were also reported for induction of DNA strand breaks in *in vitro* mammalian cell assays in five published non-guideline studies (Table 4.2-2).

   There was no evidence of an increase in unscheduled DNA synthesis (UDS) in rat primary hepatocyte cultures *in vitro* in a published study and a regulatory study (Table 4.2-2).

In vivo studies (in mammals) in somatic cells:

1. Mutagenicity tests: Both the rodent bone marrow micronucleus test and the rodent bone marrow chromosome aberration test were used in a total of 16 studies to examine mutagenic effects of glyphosate.

   In 8 regulatory studies in rats and mice conducted according to internationally agreed test guidelines, glyphosate was administered by oral gavage at dose levels up to 5000 mg/kg bw, which is well above the limit dose of 2000 mg/kg bw according to OECD test guidelines 474 or 475. The tests gave consistently negative results (Table 4.2-3).
   In another 8 studies in rats and mice (4 publications and 4 regulatory studies), glyphosate was administered by intraperitoneal application at dose levels up to 600 mg/kg bw in mice and up to 1000 mg/kg bw in rats. These dose levels may have exceeded the maximum tolerated dose, since the intraperitoneal LD_{50} of glyphosate has been reported to be 134 mg/kg bw in mice (Bababunmi et al., 1978, ASB2015-8535). For rats, the intraperitoneal LD_{50} of glyphosate ranged from 238 mg/kg bw to 1383 mg/kg bw ([redacted] 1978, ASB2015-8535, [redacted] 1991, TOX9300330). Irrespective of the high dose levels tested, negative results were obtained in 6 studies (one chromosome aberration test in rats, 5 micronucleus tests in mice; Table 4.2-3).
   In one published study in mice ([redacted] 1997, Z59299), two i.p. doses of 150 mg/kg bw, administered 24 h apart, produced a statistically significant increase in micronuclei when bone marrow was examined 24 h after the second dose. However, the dose tested was in the range of the intraperitoneal LD_{50} of glyphosate reported for mice, and no information on signs of toxicity was provided in the publication.
   In second published study in mice ([redacted] 2009a, ASB2012-11892), two i.p. doses of 200 mg/kg bw, administered 24 h apart, produced a statistically significant increase in

micronuclei when bone marrow was examined 24 h after the second dose. However, the result of this study is flawed by a major deviation from internationally agreed test guidelines: "erythrocytes" instead of immature or "polychromatic erythrocytes" (PCE) were scored for micronuclei. In an assay with the reported treatment and sampling times, scoring of all erythrocytes instead of polychromatic erythrocytes would be inappropriate (test guideline OECD 474).

2. Further *in vivo* studies: Evidence for DNA adduct formation and for induction of DNA strand breaks following i.p. administration of glyphosate to mice at a single dose of 300 mg/kg bw has been reported in one publication ([redacted] 1997, Z59299). Induction of DNA strand breaks was also reported in a published study in mice after oral doses of 40 and 400 mg/kg bw per day over a period of 14 days (Mañas et al., 2013). In contrast, no evidence for DNA adduct formation was reported following intraperitoneal administration of glyphosate isopropylammonium salt to mice at a single dose of 270 mg/kg bw ([redacted] 1998, TOX1999-318).
   Since the induction of DNA strand breaks was observed at a dose close to or in excess of the i.p. LD_{50} of glyphosate in mice, the positive result of this assay may be caused by secondary effects of cytotoxicity.

In vivo studies (in mammals) in germ cells:

Glyphosate has been shown to be devoid of mutagenic activity in a dominant lethal assay in mice at oral doses up to 2000 mg/kg bw (EPA, 1980, ASB2015-8547; [redacted] 1980, TOX9552377) and in a dominant lethal assay in rats at oral doses up to 2000 mg/kg bw ([redacted] 1992, TOX9551102).

Overall conclusion:

Glyphosate has been tested in a broad spectrum of mutagenicity and genotoxicity tests *in vitro* and *in vivo*.

In vitro, bacterial assays and mammalian cell gene mutation assays gave consistently negative results. Also, the majority of *in vitro* chromosomal aberration tests and micronucleus tests were negative, in particular, all of the studies performed under GLP conditions resulted in negative findings. *In vitro* tests for induction of indicator endpoints gave positive results for induction of SCE and DNA strand breaks (comet assay) and a negative result for induction of DNA repair (UDS).

In vivo, 14 somatic cell tests for induction of chromosomal aberrations or micronuclei gave negative results, including all the 12 regulatory studies conducted under GLP conditions. Therefore, it is concluded that glyphosate does not induce chromosomal damage *in vivo*, although positive results are reported in two publications. Furthermore, there was no evidence for mutagenic activity in germ cells. Inductions of DNA strand breaks were reported in 2 publications following a high i.p. dose or repeated oral doses.

Taking into account all available data and using a weight of evidence approach, it is concluded that glyphosate does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria.

AMPA:

AMPA has been tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in an adequate range of assays.

In vitro, two bacterial assays and a mammalian cell gene mutation assay performed under GLP conditions gave negative results, while two micronucleus tests were positive. Two *in vitro* tests for induction of DNA repair (UDS) performed under GLP conditions gave negative results; while a test for induction of DNA strand breaks (comet assay) was positive.

In vivo, two bone marrow micronucleus tests conducted under GLP conditions gave negative results,

while a positive result was reported in a published study flawed by methodological limitations. Induction of DNA strand breaks was reported in a publication following repeated oral doses.

Taking into account all available data and using a weight of evidence approach, it is concluded that AMPA does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria.

Glyphosate-based formulations:

Glyphosate-based formulations have been extensively tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in a wide range of assays. However, since formulation compositions are considered proprietary, the specific composition of the formulations tested was not available for the published studies.

In vitro, bacterial assays gave generally negative results. No regulatory studies of glyphosate-based formulations in *in vitro* mammalian cell chromosomal aberration or micronucleus assays were provided. However, published studies suggested the possibility of activity of glyphosate-based formulations in *in vitro* chromosomal damage assays. No regulatory studies of glyphosate-based formulations in *in vitro* mammalian cell assays for DNA damage were provided. In some published studies, however, positive results for DNA strand breakage and SCE induction were reported.

In vivo mammalian chromosomal aberration or micronucleus assays gave positive results in some published studies for specific glyphosate-based formulations. However, no regulatory studies for these endpoints were provided. Also, no regulatory studies for these endpoints were provided for *in vivo* mammalian assays for DNA damage. However, in some published studies positive results for DNA adducts, DNA strand breakage and SCE induction were reported for specific glyphosate-based formulations. The positive results may be associated with high organ toxicity (liver, kidney) that was primarily due to the non-glyphosate components of the formulation when administered at very high doses via the i.p. route of exposure.

In non-mammalian systems, positive results were reported in *in vivo* studies on chromosomal damage or DNA damage of fish, amphibians and reptiles with different formulations (IARC monograph, Table 4.5). For the representative formulation for the EU renewal procedure 'Roundup Ultra' two studies ([redacted] 2012, ASB2014-7619, [redacted] 2014, ASB2015-8631) reported positive results in comet assays using the European eel as test species.

However, in addition to some technical limitations, there is considerably less experience with these assay systems, and their relevance fur human health assessment is undecided.

Table 4.2-1: Glyphosate; mutagenicity tests in mammalian cells or bacteria *in vitro*

Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range	GLP, Test guideline	RAR 04/2015	Comments BfR
[redacted] 2009a, ASB2012-11892	Yes	Human Lymphocytes (Chromosomal damage)	Chromosomal aberrations	–	NT	0.2-6.0 mM (34 - 1015 µg/mL) Purity: 96%	NR, TG 473	p. 401, 436	Only 100 cells scored per treatment. Results not reported separately for replicate cultures.
[redacted] 1998, TOX2000-1995	No	Human lymphocytes (Chromosomal damage)	Chromosomal aberration	–	–	-S9/+S9: 100 - 1250 µg/ml Purity: 95.6%	GLP, TG 473	p. 345, 353-357	
[redacted] 2009a, ASB2012-11907	Yes	Human lymphocytes (Chromosomal damage)	Micronucleus formation	–	(+)	-S9/+S9: 0.5 - 580 µg/mL Purity: 98%	Non-GLP, NR	p. 401, 437	$P < 0.01$ (580 µg/mL) Independent coding of slides for scoring not indicated for visually scored slides. Results not reported separately for replicate cultures.
[redacted] 1995, TOX9651525	No	Human lymphocytes (Chromosomal damage)	Chromosomal aberration	–	–	-S9: 33 - 333 µg/mL +S9: 237 - 562 µg/mL Purity: 96%	GLP, TG 473	p. 345	
[redacted] 1996, ASB2012-11476	No	Chinese hamster lung cells (Chromosomal damage)	Chromosomal aberrations	–	–	-S9/+S9: 312.5 - 1250 µg/mL Purity: 95.3%	GLP, NR	p. 345, 351-353	
[redacted] 1995, ASB2012-11475	No	Chinese hamster lung	Chromosomal aberrations	–	–	-S9: 62.5 -	GLP, TG 473	p. 345-351	

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Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range	GLP, Test guideline	RAR 04/2015	Comments BfR
		cells (Chromosomal damage)				500 µg/mL +S9: 250 - 1000 µg/mL Purity: 95.7%			
[redacted] 1998, ASB2013-9836	Yes	Bovine Lymphocytes (Chromosomal damage)	Chromosomal aberrations	+	NT	17 - 170 µM (3 - 30 µg/mL) Purity: ≥ 98%	NR	p. 387	$P < 0.05$ (17 µM) 150 metaphases per concentration were scored for CAs (200 or 300 needed acc. TG 1997 or 2014).
[redacted] 2014, ASB2014-8086	Yes	Hamster, Chinese CHO-K1 ovary cell line (Chromosomal damage)	Micronucleus formation	–	+	5 - 100 µg/mL Purity: not given	NR	p. 423-424	$P \leq 0.001$ (10 µg/mL) No continuous treatment (TG 2014).
[redacted] 1996, TOX2000-1994	No	Mouse lymphoma cells /L5178Y TK$^{+/-}$ (Mutation)	Mouse lymphoma test	–	–	+/-S9: 296 - 1000 µg/mL Purity: 95.6%	GLP, TG 476	p. 338-341	
[redacted] 1991, TOX9552372	No	Mouse lymphoma cells/L5178Y	Mouse lymphoma test	–	–	-S9: 0.61 - 5.0 mg/mL +S9: 0.52 - 4.2 mg/mL Purity: 98.6%	GLP, TG 476	p. 338	
[redacted] 1988, TOX9500253	Yes	Hamster, Chinese CHO-K1BH4 ovary,	*Hprt* mutation	–	–	-S9: 2 - 22.5 mg/mL +S9:	NR	p. 338	Not entirely clear from the original study report which dose level was actually the highest under activation conditions.

ED_001487B_00000719-00054

Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range	GLP, Test guideline	RAR 04/2015	Comments BfR
also reported in RAR, TOX9552369, Z35243		cell line (Mutation)				5 - 22.5 or 25 mg/mL Purity: 98.7%			
[redacted] 1988, TOX9500253	Yes	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 (Mutation)	Reverse mutation	–	–	10 - 5000 µg/plate Purity: 98.4%	NR	p. 305	2-aminoanthracen only used as positive control + S9. Only duplicate plating.
[redacted] 1988, TOX9500253	Yes	Escherichia coli WP2 (Mutation)	Reverse mutation	–	–	10 - 5000 µg/plate Purity: 98.4%	NR	p. 305	2-aminoanthracen only used as positive control + S9. Only duplicate plating.

Results: +, positive; -, negative
NT, not tested; NR, not reported ; S9, 9000 × g supernatant; Hprt, hypoxanthine guanine phosphoribosyl transferase gene;

Table 4.2-2: Glyphosate; genotoxicity tests in mammalian cells or bacteria *in vitro*

Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range, purity of test substance	GLP, Test guideline	RAR 04/2015	Comments BfR
[redacted] 2009a, ASB2012-11892	Yes	Liver Hep-2 (DNA damage)	DNA strand breaks, comet assay	+	NT	3 - 7.5 mM (507.2 - 1268 µg/mL) Purity: 96%	NR	p. 404, 436	$P < 0.01$ (507.2 µg/mL), dose–response relationship No indication of pH or osmolality control. Results not reported separately for replicate cultures.

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Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range, purity of test substance	GLP, Test guideline	RAR 04/2015	Comments BfR
[redacted] 2009b, ASB2012-11906	Yes	Human lymphocytes (DNA damage)	DNA strand breaks, standard and hOGG1 modified comet assay	+	+	0.5-580 µg/mL Purity: 98%	NR	p. 437	$P < 0.05$ (3.5 µg/mL) With the hOGG1 modified comet assay, + S9, the increase was significant ($P < 0.01$) only at the highest dose tested (580 µg/mL). No indication of pH or osmolality control. Results not reported separately for replicate cultures. Authors state that no clear dose-dependent effect was observed.
[redacted] 2014, ASB2014-6902	Yes	Human lymphocytes (DNA damage)	DNA strand breaks, comet assay	+	NT	0.0007-0.7 mM (0.118- 118 µg/mL) Purity: 96%	NR	p. 404	$P \leq 0.01$ (0.0007 mM) No indication of pH or osmolality control. Results not reported separately for replicate cultures. Inconsistent and not clear dose dependent. Test was conducted with glyphosate isopropylamine .
[redacted] 2005, ASB2012-11910	Yes	Fibroblast GM 39 and Fibrosarcoma HT1080 (DNA damage)	DNA strand breaks, comet assay	+	NT	4.0-6.5 nM ($6.76 \cdot 10^{-4}$ – $1.1 \cdot 10^{-3}$ µg/mL, GM39 cells), 4.5-6.5 nM ($7.6 \cdot 10^{-4}$-$1.1 \cdot 10^{-3}$ µg/mL HT1080) cells) Purity: not given	NR	p. 403	Fibroblast: $P < 0.001$ (4 nM) Fibrosarcoma: $P < 0.001$ (4.75 nM) No indication of pH or osmolality control. No concurrent measurement of toxicity reported. Independent coding of slides for scoring not indicated for visually scored slides. Results not reported separately for replicate cultures. Concentrations seem very low.
[redacted] 2004, ASB2012-11886	Yes	Fibroblast GM 5757 (DNA damage)	DNA strand breaks, comet assay	(+)	NT	75 mM (12.7 mg/ml) Purity: 98.4%	NR	–	Not regarded as glyphosate was only tested together with H_2O_2.
Koller et al.,	Yes	Buccal	DNA strand	+	NT	10-2000 µg/mL	NR	p. 404	$P \leq 0.05$ (20 µg/mL)

ED_001487B_00000719-00056

Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range, purity of test substance	GLP, Test guideline	RAR 04/2015	Comments BfR
2012, ASB2014-7618		carcinoma TR146 (DNA damage)	breaks, comet assay			Purity: 95%			No indication of pH or osmolality control. Results not reported separately for replicate cultures. No clear dose-response effect. Higher activity of formulation than pure a. s.
[redacted] 1997, Z59299	Yes	Human lymphocytes (Chromosomal damage)	Sister-chromatid exchange	+	NT	0.33 and 6 mg/mL Purity: 99.9%	NR	p. 385, 390, 429	$P < 0.05$ (1 mg/ml) The number of only two subjects to be included in the study appears too low for meaningful evaluation. Furthermore, the data from two experiments were pooled for the two donors and individual values were not given. The study is performed with methodological and reporting deficiencies (no positive controls included in *in vitro* SCE). Test guideline deleted by now.
[redacted] 1988, TOX9500253	Yes	Rat, Fisher F334 Hepatocytes (DNA damage)	Unscheduled DNA synthesis	–	NT	$1.25 \cdot 10^{-5}$-$1.25 \cdot 10^{-1}$ mg/ml Purity: 98%	NR	–	Only between 5 and 20 cells counted. Test guideline deleted by now.
[redacted] 1994, TOX9400697	No	UDS assay/ Primary rat hepatocytes/Sprague Dawley	Unscheduled DNA synthesis	–	NT	0.2-111.7 mM (33.8 µg/ml-18.9 mg/ml) Purity: > 98%	GLP, TG 482	p. 342	Instead of autoradiography or LSC procedures, incorporation of radioactivity into DNA was determined on basis of UV absorbance measurement.
[redacted] 1998, ASB2013-9836	Yes	Bovine Lymphocytes (Chromosomal damage)	Sister-chromatid exchange	+	NT	17-170 µM (2,9-29 µg/ml Purity: ≥ 98%	NR	p. 387	$P < 0.05$ (17 µM) Data is pooled for the three donors and individual values were not given. Increase of SCE not dose related in highest dose group.

ED_001487B_00000719-00057

Reference	Evaluated by IARC	Test system (endpoint)	Test	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range, purity of test substance	GLP, Test guideline	RAR 04/2015	Comments BfR
									Test guideline deleted by now.
[redacted] 1995, ASB2012-11477	No	B. subtilis H17, M45 (DNA damage/repair)	Rec assay	–	–	7.5-240 µg/disk Purity: 95.7%	GLP, U.S. EPA FIFRA	p. 342-344	Rec assay is not a standard method for this endpoint (DNA damage and repair).

Results: +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality
hOGG1, human 8-hydroxyguanosine DNA-glycosylase; NR, not reported; NT, not tested; S9, 9000 × g supernatant; vs, versus

Table 4.2-3: Glyphosate; somatic cell mutagenicity tests in mammals, *in vivo*

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
Oral application								
[redacted] 1991, TOX9552374	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 98.6 % oral, 1x 0 or 5000 mg/kg bw, sampled after 24, 48 and 72 h	Negative	GLP, OECD 474 (1983)	*MN/2000 PCE [mean (range)]:* Control: 2.7 (1-4) 24h, 5000 mg/kg: 3.2 (1-5) 48h, 5000 mg/kg: 2.8 (1-6) 72h, 5000 mg/kg: 1.7 (0-4) PosControl: 48.2 (32-58)	5 animals per sex and sampling time. 2000 PCE scored/animal. PCE/NCE: no effect.	p. 358, 364
[redacted] 1993, TOX9551100	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 96.8 % oral, 2x 0, 50, 500 or 5000 mg/kg bw (24 h interval), sampled 24 h after second dose	Negative	GLP, OECD 474 (1984)	*% MNPCE [mean (range)], male/female:* Control: 0.69 (0.1-1.6)/0.51 (0.2-1.0) 50 mg/kg: 0.84 (0.2-1.4)/0.28 (0.0-0.5) 500 mg/kg: 0.73 (0.4-1.6)/0.52 (0.2-1.3) 5000 mg/kg: 0.89 (0.7-1.1)/1.05*(0.4-1.6) PosControl: 2.33* (1.5-3.2)/2.39* (1.4-3.4)	5 animals per sex and dose (Control: 10/sex). 2000 PCE scored/animal. PCE/NCE: no effect (but PosControl). *The MN incidence in females at 5000 mg/kg is within the range of controls considering both sexes.*	p. 357 ff.

ED_001487B_00000719-00058

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
						*p<0.05		
[redacted] 1994, TOX9400323	No	Mouse, Chromosome aberration test, bone marrow	Glyphosate, 96.8 % oral, 2 x 0-5000 mg/kg bw (24 h interval), sampled 24 h after second dose	Negative	GLP, OECD 475 (1984)	*No. of aberrations per 250-250-500 metaphases (male/female/total)* Control: 12/10/22 5000 mg/kg: 10/11/21 PosControl: 139*/155*/294* *p<0.05	5 animals per sex. 50 metaphases/animal examined. *Mitotic index (%) (male/female/total)* Control: 13.3/17.4/15.3 5000 mg/kg: 8.9*/9.5*/9.2* PosControl: 14.7/5.5*/10.1*	p. 358
[redacted] 1996, TOX2000-1996	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 95.6 % oral, 1x 0 or 5000 mg/kg bw, sampled after 24 and 48 h	Negative	GLP, OECD 474 (1997)	*MN/1000 PCE (mean±SD), male/female:* 24h, Control: 1.6±0.8/1.4±0.7 24h, 5000 mg/kg: 2.1±1.6/2.1±2.5 24h, PosControl: 22.2±6.1*/23.3±4.9* 48h, Control: 1.7 ±1.3/0.7±0.6 48h, 5000 mg/kg: 2.1±1.9/0.8±0.8 *p<0.01	5 animals per sex and sampling time. 2000 PCE scored/animal. PCE/NCE: no effect.	p. 359, 370 ff.
[redacted] 2008, ASB2012-11483	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 99.1 % oral, 1x 0, 500, 1000 or 2000 mg/kg bw, sampled after 24 h 1x 0 or 2000 mg/kg bw, sampled after 48 h	Negative	GLP, OECD 474 (1997)	*MN/2000 PCE [mean (range)]:* 24h, Control: 1.4 (0-3) 24h, 500 mg/kg: 1.6 (1-2) 24h, 1000 mg/kg: 1.6 (1-2) 24h, 2000 mg/kg: 1.4 (0-2) 24h, PosControl: 63.0 (44-92)* 48h, Control: 1.4 (0-3) 48h, 2000 mg/kg: 1.6 (0-3) *p<0.01	5 males per group and sampling time. 2000 PCE scored/animal. PCE/NCE: no effect. Historical control data (293 studies): *% MNPCE [mean±SD, (range)]: 0.084±0.031 (0.01 – 0.18)*	p. 359, 372 ff.
[redacted] 2012, ASB2014-9277	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 98.9 % oral, 2x 0 or 2000 mg/kg bw (24 h interval), sampled 24 h after second dose	Negative	GLP, OECD 474 (1997)	*% MNPCE [mean (range)]:* Control: 0.033 (0-0.05) 2000 mg/kg: 0.0 (0-0) PosControl: 2.49* (1.1-3.7) *p<0.01	6 males per group. 2000 PCE scored/animal. PCE/NCE: no effect at 2000 mg/kg, increased in PosControl. Historical control data (of 73 studies)	p. 359, 374 ff.

ED_001487B_00000719-00059

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
							% MNPCE [mean±SD (range)]: *0.02±0.02 (0.0-0.07)*	
[redacted] 2012, ASB2014-9333	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 96.3 % oral, 1x 0 or 2000 mg/kg bw, sampled after 24 and 48 h	Negative	GLP, OECD 474 (1997)	*MN/2000 PCE [mean±SD, (range)]:* 24h, Control: 3.2±3.6 (0-8) 24h, 2000 mg/kg: 2.3±0.5 (2-3) 24h, PosControl: 40.2±18.2* (16-67) 48h, Control: 1.4±1.1 (0-3) 48h, 2000 mg/kg: 1.1±1.3 (0-3) *p<0.01	7 males per group (Control and PosControl: 5 males each). 2000 PCE scored/animal. PCE/NCE: no effect. Historical control data (of 219 studies) *% MNPCE [mean±SD (range of mean group value)]:* 0.108±0.039 (0.01-0.25)	p. 359. 375 ff.
[redacted] 2009, ASB2012-11479	No	Rat, Micronucleus test, bone marrow	Glyphosate, 98.8 % oral, 1x 0, 500, 1000 or 2000 mg/kg bw, sampled after 24 and 48 h	Negative	GLP, OECD 474 (1997)	*MN/2000 PCE (mean±SD), male/female:* 24h, Control: 1.6±1.1/1.8±0.4 24h, 500 mg/kg: 1.0±1.2/1.2±1.3 24h, 1000 mg/kg: 0.8±0.4/1.6±0.9 24h, 2000 mg/kg: 1.2±0.8/0.8±0.8 24h, PosControl: 30.2±10.5*/24.0±4.9* 48h, Control: 2.0 ±1.9/2.2 ±1.3 48h, 2000 mg/kg: 1.6±0.9/0.8±0.8 *p<0.05	5 animals per sex and dose and sampling time. 2000 PCE scored/animal. PCE/NCE: no effect. Historical control data (24, 48 and 72 h samplings combined): *MN/1000 PCE [mean and (range):* Males: 1.97 (0.4 – 5.7) Females: 1.86 (0.4 – 4.7)	p. 359. 376 ff.
i.p. application								
[redacted] 1988, TOX9500253 [redacted] 1983, TOX9552369	Yes	Rat, Chromosome aberration test, bone marrow	Glyphosate, 98 % i.p., 1x 0 or 1000 mg/kg bw, sampled after 6, 12 and 24 h	Negative	No GLP, no reference to TG	*% aberrant cells (mean), male/female/total:* 6h, Control: 1.3/2.7/2.0 6h, 1000 mg/kg: 2.3/3.0/2.7 12h, Control: 1.0/1.5/1.2 12h, 1000 mg/kg: 2.0/2.5/2.3 24h, Control: 1.3/2.3/1.8 24h, 1000 mg/kg: 1.0/3.7/2.6 PosControl: 42.2*/23.8*/40.8*	Consistent with OECD 475 (1984): 6 animals per sex and sampling time. Ca 50 metaphases/animal examined. Slides were coded and scored "blind".	p. 358, 383

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Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
						* p < 0.05	Original study reported in RAR as Li, 1983 (TOX9552375).	
[redacted] 1993, Z82234	Yes	Mouse, Micronucleus test, bone marrow	Glyphosate isopropylamine salt, purity not stated i.p., 1x 0, 100, 150 or 200 mg/kg bw sampled after 24 and 48 h	Negative	No GLP, no reference to TG	*% MNPCE (mean±SD):* 24h, Control: 0.27±0.11 24h, 100 mg/kg: 0.20±0.13 24h, 150 mg/kg: 0.2±0.13 24h, 200 mg/kg: 0.25±0.10 24h, PosControl: 2.53±0.59 48h, 150 mg/kg: 0.13±0.09 48h, 200 mg/kg: 0.12±0.09	Consistent with OECD 474 (1983): Mostly 5 animals per sex and dose and sampling time. 1000 PCE scored/animal. Slides were scored randomly. PCE/NCE: no effect.	p. 385, 388f.
[redacted] 997, Z59299	Yes	Mouse, Micronucleus test, bone marrow	Glyphosate, 99.9 % i.p., 2x 150 mg/kg bw (24 h interval), sampled 6 or 24 h after second dose	Positive	No GLP, no reference to TG	*MN/1000 PCE (mean±SD):* Control: 0.75±0.46 6h, 2x 150 mg/kg: 1.4±0.9 24h, 2x 150 mg/kg: 2.4±1.5* 24h, PosControl: 80.0±8.5* * p < 0.05	6 males in Control and PosControl group. 3000 PCE scored/animal. PCE/NCE: 0.73±0.06 in Control, 0.6±0.05 at 6h, 0.5±0.2 at 24h. *Deviations from OECD 474 (1997):* *Only 3(4) males examined per sampling time.* *Sampling time of Control not stated.* *Independent coding of slides not stated.*	p. 385, 389
[redacted] 2009a, ASB2012-11892	Yes	Mouse, Micronucleus test, bone marrow	Glyphosate, 96 % i.p., 2x 50, 100 or 200 mg/kg bw (24 h interval), sampled 24 h after second dose	Positive	No GLP, OECD 474 (1997)	*MN/1000 **Erythrocytes** (mean±SD):* Control: 3.8 ±0.8 2x 50 mg/kg: 3.7±0.5 2x 100 mg/kg: 4.2±0.5 2x 200 mg/kg: 13.0±3.5* PosControl: 19.2±3.9* * *P* < 0.01	5 animals per dose. PCE/NCE no effect. *Deviations from OECD 474 (1997):* *Sex of animals not reported.* *1000 **erythrocytes** (not **PCE**) scored/animal.* *Independent coding of slides not stated.*	p. 402, 410

ED_001487B_00000719-00061

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
[redacted] 1999, ASB2012-11482	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 95 % i.p., 2x 0, 187.5, 375 or 562.5 mg/kg bw (24 h interval), sampled 24 h after second dose	Negative	GLP, internal SOP	*MN/1000 PCE [mean (range)], male/female:* Control: 0.4 (0-1)/0.8 (0-2) 188 mg/kg: 0.0 (0)/0.6 (0-3) 375 mg/kg: 0.6 (0-3)/0.6 (0-2) 563 mg/kg: 0.4 (0-2)/0.6 (0-1) PosControl: 4.8* (4-7)/4.8* (2-12) *p<0.05	5 animals per sex and dose. 1000 PCE and 1000 NCE scored per animal. PCE/NCE: no effect (but PosControl). MN/1000 NCE: no effect (but PosControl). *$LD50_{i.p.}$=750 mg/kg*	p. 358, 367 ff.
[redacted] 2006, ASB2012-11478	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 95.7 % i.p., 1x 0, 150, 300 or 600 mg/kg bw, sampled after 24 and 48 h	Negative	GLP, OECD 474 (1997)	*% MNPCE [mean±SD, (range)]:* 24h, Control: 0.06±0.06 (0.0-0.15) 24h, 150 mg/kg: 0.07±0.04 (0.0-0.10) 24h, 300 mg/kg: 0.06±0.05 (0.0-0.15) 24h, 600 mg/kg: 0.19±0.07* (0.05-0.25) 24h, PosControl: 3.03±0.49*** (2.20-3.35) 48h, Control: 0.1±0.12 (0.0-0.35) 48h, 600 mg/kg: 0.09±0.11 (0.0-0.30) *p<0.05, ***p<0.001	7 males per group and sampling time. 2000 PCE scored/animal. *Pre-test: Mortality at 800-1000 mg/kg, clinical signs at 150 mg/kg and above.* PCE/NCE: reduced at 600 mg/kg (not in PosControl). Stat. sign. increase in MNPCE at 600 mg/kg (24 h), within historical control. *Control data from 60 groups (24h):* *0.0-0.9 MN/1000 PCE: 40x (67%)* *1.0-1.4 MN/1000 PCE: 14x (23%)* *1.5-2.0 MN/1000 PCE: 3x (5%)* *2.1-2.5 MN/1000 PCE: 3x (5%)*	p. 358, 359 ff.
[redacted] ASB2012-11481	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 98 % i.p., 2x 0, 15.6, 31.3 or 62.5 mg/kg bw (24 h interval),	Negative	GLP, OECD 474 (1997)	*MN/2000 PCE [mean (range)], male/female:* Control: 0.0 (0)/0.0 (0) 15.6 mg/kg: 0.0 (0)/0.0 (0) 31.3 mg/kg: 0.0 (0-1)/0.0 (0)	5 animals per sex and dose. 2000 PCE scored/animal. *Pre-test: Mortality at 500-1000 mg/kg, decreased PCE/NCE at 250 mg/kg and above.*	p. 358. 364 ff.

ED_001487B_00000719-00062

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
			sampled 24 h after second dose			62.5 mg/kg: 0.6 (0-3)/0.0 (0) PosControl: 23.0* (8-30)/12.2* (7-26) *p<0.01	PCE/NCE no effect. Historical control: ca. 3 MN/1000 PCE	
[redacted] 2010, ASB2014-9284	No	Mouse, Micronucleus test, bone marrow	Glyphosate, 98 % i.p., 2x 0, 125, 250 or 375 mg/kg bw (24 h interval), sampled 24 h after second dose	Negative	GLP, OECD 474 (1997)	*MN/2000 PCE [mean (range)], male/female:* Control: 0.4 (0-2)/0.4 (0-1) 125 mg/kg: 0.2 (0-1)/0.0 (0-1) 250 mg/kg: 0.0 (0)/0.0 (0) 375 mg/kg: 0.2 (0-1)/0.0 (0-1) PosControl: 8.0* (5-11)/6.4* (5-9) *p<0.01	5 animals per sex and dose. 2000 PCE scored/animal. *Clinical signs at 125 mg/kg and above.* PCE/NCE: slight increase at 250 and 375 mg/kg and in PosControl. Historical control: ca. 3 MN/1000 PCE	p. 358. 364 ff.

NCE, normochromatic erythrocytes; MN, micronucleus; MNPCE%, percent of micronucleated polychromatic erythrocytes; PCE, polychromatic erythrocytes; SD, standard deviation

Table 4.2-4: Glyphosate; further tests on DNA adducts and DNA strand breaks in mammals, *in vivo*

Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
[redacted] 1997, Z59299	Yes	Mouse DNA adduct (8-OHdG by LC/UV), liver	Analytical grade glyphosate (purity 99.9 %) i.p.; 1 × 300 mg/kg bw; sampled after 8 and 24 h	- (4 h) + (24 h)	No GLP, no reference to TG	(Estimated from figure in report) Control: approx. 0.6 moles 8-OHdG/10^5 moles dG 4 h: approx. 0.9 moles 8-OHdG/10^5 moles dG 24 h: approx. 3.6 moles 8-OHdG/10^5 moles dG*	3 male animals per group, at least 3 independent repeat experiments	p. 386
[redacted] 1997, Z59299	Yes	Mouse DNA adduct (8-OHdG by LC/UV),	Analytical grade glyphosate (purity 99.9 %) i.p.; 1 × 300 mg/kg bw; sampled after 8 and 24 h	– (4 & 24 h)	No GLP, no reference to TG	(Estimated from figure in report) Control: approx. 0.6 moles 8-OHdG/10^5 moles dG	3 male animals per group, at least 3 independent repeat experiments	p. 386

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Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
		kidney				4 h: approx. 0.5 moles 8-OHdG/10^5 moles dG 24 h: approx. 0.4 moles 8-OHdG/10^5 moles dG*		
[redacted] 1998, TOX1999-318	Yes	Mouse DNA adduct (^{32}P-DNA post labelling), kidney	Glyphosate isopropylammonium salt i.p.; 1 × 0, 130 or 270 mg/kg bw; sampled after 24 h	–	No GLP, no reference to TG	Not reported	6 animals in control group, 6 in low dose group and 3 in high dose group, sex of animals not clear	p. 386
[redacted] 1998, TOX1999-318	Yes	Mouse DNA adduct (^{32}P-DNA post labelling), liver	Glyphosate isopropylammonium salt i.p.; 1 × 0, 130 or 270 mg/kg bw; sampled after 24 h	–	No GLP, no reference to TG	Not reported	6 animals in control group, 6 in low dose group and 3 in high dose group, sex of animals not clear	p. 386
[redacted] 1997, Z59299	Yes	Mouse DNA strand breaks (alkaline elution assay), liver	Analytical grade glyphosate (purity 99.9 %) i.p.; 1 × 300 mg/kg bw; sampled after 4 and 24 h	+ (4 h) - (24 h)	No GLP, no reference to TG	(Estimated from figure in report) Control: approx. 15 *10^3/mL 4 h: approx. 47 *10^3/mL* 24 h: approx. 20 *10^3/mL	3 male animals per group, at least 4 independent repeat experiments	p. 385
[redacted] 1997, Z59299	Yes	Mouse DNA strand breaks (alkaline elution assay), kidney	Analytical grade glyphosate (purity 99.9 %) i.p.; 1 × 300 mg/kg bw; sampled after 4 and 24 h	+ (4 h) - (24 h)	No GLP, no reference to TG	(Estimated from figure in report) Control: approx. 17 *10^3/mL 4 h: approx. 55 *10^3/mL* 24 h: approx. 25 *10^3/mL	3 male animals per group, at least 4 independent repeat experiments	p. 385
[redacted] 2013, ASB2014-	No	Mouse comet assay,	Glyphosate (96%) Drinking water, 14 days, 0, 40 or	+	No GLP, no	Tail moment (mean ± SEM): Control: 2.98±1.08	6 animals per group	p. 404

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Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
6909		blood cells	400 mg/kg bw per day; sampled after treatment period		reference to TG	40 mg/kg bw per day: 8.54***±7.82 400 mg/kg bw per day: 9.06***±5.15	sex of animals not clear	
[redacted] 2013, ASB2014-6909	N	Mouse comet assay, liver cells	Glyphosate (96%) Drinking water, 14 days, 0, 40 or 400 mg/kg bw per day; sampled after treatment period	+	No GLP, no reference to TG	Tail moment (mean ± SEM): Control: 7.14±3.41 40 mg/kg bw per day: 7.92*±3.99 400 mg/kg bw per day: 20.59***±15.47	6 animals per group sex of animals not clear	p. 404

8-OHdG, 8-hydroxy-2' -deoxyguanosine; dG, deoxyguanosine; SEM, standard error of the mean; SCGE, single cell gel electrophoresis

Table 4.2-5: Glyphosate; germ cell mutagenicity tests in mammals, *in vivo*

Reference	In IARC mono-graph	Species, test, tissue	Test substance, purity, application route, dose levels, mating period	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
EPA, 1980, ASB2015-8547 [redacted] 1980, TOX9552377	Yes	Mouse, Dominant lethal test	Glyphosate, 98.7 % oral, 1x 0, 200, 800 or 2000 mg/kg bw 8 successive one-week mating periods (1 male/2 females)	Negative	GLP, no reference to TG	No increase in post-implantation loss in treated groups. PosControl: stat. significant increase in post-implantation loss.	Only 10 males per group. Post-implantation loss evaluated after mating of non-treated females with glyphosate-treated male mice. Original study reported in RAR as [redacted] (1980, TOX9552377).	p. 378
[redacted] 1992, TOX9551102	No	Rat, Dominant lethal test	Glyphosate, 96.8 % oral, 1x 0, 200, 800 or 2000 mg/kg bw 10 successive one-week mating periods (1 male/1 female)	Negative	GLP, OECD 478 (1984)	No increase in post-implantation loss in treated groups. PosControl: stat. significant increase in post-implantation loss.	30 males per group (Control: 10 males, PosControl: 2 x 5 males). Post-implantation loss evaluated after mating of non-treated females with glyphosate-treated male mice.	p. 378

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Table 4.2-6: AMPA; mutagenicity and genotoxicity tests, *in vitro*

Reference	Evaluated by IARC	Test system (endpoint)	Test substance	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range	GLP, Test guideline	RAR 04/2015	Comments BfR
[redacted] 1988, TOX9500043	No	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 (reverse mutation)	AMPA, >99%	Negative	Negative	1.6-5000µg/plate	GLP, OECD 471 (1983)	p. 735	No evidence of genotoxicity. The slight increase in revertant numbers in one strain in the first experiment was rather weak and was sufficiently contravened by subsequent trials in which the test material proved clearly negative.
[redacted] 1993, TOX9300378	No	Salmonella typhimurium TA1535, TA1537, TA98, TA100 (reverse mutation)	AMPA, 99.2%	Negative	Negative	310-5000µg/plate	GLP, OECD 471 (1983)	p. 95, 727	
[redacted] 1993; TOX9300380	No	L5178Y mouse lymphoma cells, gene mutation, TK locus	AMPA, 99.2%	Negative	Negative	310-5000µg/mL	GLP, OECD 476 (1983)	p. 727	
[redacted] 2009b, ASB2012-11891	Yes	Human lymphocytes, Chromosomal aberrations	Analytical grade AMPA (99%).	Positive	NT	1.8 mM [200 µg/mL] $P < 0.05$	No GLP, no reference to TG		Methodological deficiencies (only 2 dose levels used).
[redacted] 2014, ASB2014-	Yes	CHO cells, Micronucleus formation	AMPA, purity not stated	Positive	Positive	-S9: 0.005-0.1 µg/ml +S9: 0.1-5 µg/ml	No GLP, no reference	p. 423	-S9: ≥0.01 µg/mL $P < 0.05$ +S9: ≥0.1 µg/mL $P < 0.01$

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Reference	Evaluated by IARC	Test system (endpoint)	Test substance	Results: Without metabolic activation by authors	Results: With metabolic activation by authors	Concentration range	GLP, Test guideline	RAR 04/2015	Comments BfR
8086							to TG		
[redacted] 1991, TOX9552409	No	Primary rat hepatocytes (Fischer F334) (UDS test)	AMPA, 94.38%	Negative	Negative	5-5000µg/mL	GLP, no reference to TG	p. 728, 962 steht nur in der Über-sichts-tabelle	Negative up to 2500 µg/mL, meaningful evaluation of higher concentrations not possible due to cytotoxicity.
[redacted] 2002, ASB2012-11508	No	Primary rat hepatocytes (Fischer) (UDS test)	AMPA, 99.9%	Negative	Negative	0.625 – 10 mM	GLP, OECD 482 (1986)	p. 728, 743	Negative under the condition of the experiment
[redacted] 2009b, ASB2012-11891	Yes	Liver Hep-2, DNA strand breaks, comet assay	Analytical grade AMPA (99%).	Positive	NT	Range 2.5-7.5 µM $P < 0.05$ at 4.5 mM [500 µg/mL]; $P < 0.01$ at up to 7.5 mM Dose–response relationship ($r \geq 0.90$; $P < 0.05$)	No GLP, no reference to TG	p. 422, 434	

Results: +, positive; -, negative
NT, not tested; NR, not reported ; S9, 9000 × g supernatant; Hprt, hypoxanthine guanine phosphoribosyl transferase gene;

Table 4.2-7: AMPA; mutagenicity and genotoxicity tests in mammals, *in vivo*

Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
[redacted]	Yes	Mouse	Analytical grade	Positive	No GLP,	MNE/1000 analysed cells:	5 animals per group	p. 422, 434

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Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
2009b, ASB2012-11891		micronucleus test, bone marrow	AMPA (purity 99 %) i.p.; 2 × 100 or 200 mg/kg bw per day; sampled 24 h after second injection		OECD 474 (1997)	Control: 3.8 ±1.8 100 mg/kg bw: 10.0**±1.9 200 mg/kg bw: 10.4**±3.3 PosControl: 19.2**±3.9 PCE/NCE: Control: 0.85±0.17 100 mg/kg bw: 1.14±0.22 200 mg/kg bw: 1.07±0.04 PosControl: 0.80.+-0.20	Sex of animals not reported. *1000 erythrocytes (not PCE) scored/animal.* *Independent coding of slides not stated.*	
[redacted] 1993, TOX9300379	No	Mouse micronucleus test, bone marrow	AMPA (99.2 %) oral; 1x 5000 mg/kg bw; sampled after 24, 48 and 72 h	Negative	GLP, OECD 474 (1983)	MN/1000 PCE [mean (range)] Control: 0.50 (0-1) 24 h, 5000 mg/kg: 0.20 (0-1) 48 h, 5000 mg/kg: 0.40 (0-1) 72 h, 5000 mg/kg:: 0.60 (0-1) PosControl: 13.1** (10-19)	5 males and 5 females per group. 1000 PCE scored/animal. 1000 NCE scored/animal	728 (mentioned but not reported in detail)
[redacted] 1993, TOX9552413 Study also mentioned by [redacted] 2000, ASB2012-12053	No	Mouse micronucleus test, bone marrow	AMPA (94.38 %) i.p.; 1x 100, 500, 1000 mg/kg bw; sampled 24, 48 and 72 h	Negative	GLP, OECD 474 (1983)	Mean MN/1000 PCE 24 h, males/females: Control: 0.2±0.4/1.0±1.4 100 mg/kg bw: 0.2±0.4/0.8±0.8 500 mg/kg bw: 0.1±0.3/2.0±2.9 1000 mg/kg bw: 0.8±1.3/0.8±0.8 PosControl: 18.3**±10.9/12.0*±12.3 48 h, males/females: Control: 0.6±1.3/0.4±0.9 100 mg/kg bw: 0.0±0.0/0.2±0.4 500 mg/kg bw: 0.6±0.9/0.2±0.4 1000 mg/kg bw: 0.2±0.4/0.0±0.0 72 h, males/females: Control: 0.2±0.4/0.0±0.0 100 mg/kg bw: 0.0±0.0/1.6*±1.1	5 males and 5 females per group. 1000 PCE scored/animal. *Pre-test: Mortality at 606 mg/kg and above*	728 (mentioned but not reported in detail)

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Reference	In IARC monograph	Species, test, tissue	Test substance, purity, route, dose levels, sampling time	Results by authors	GLP, Test guideline	Result details	Comments BfR	In RAR 04/2015
						500 mg/kg bw: 0.0±0.0/0.8±0.8 1000 mg/kg bw: 0.0±0.0/0.4±0.9		
[redacted] 2013, ASB2014-6909	N	Mouse comet assay, blood cells	AMPA (99%) Drinking water, 14 days, 0 or 100 mg/kg bw per day; sampled after treatment period	Positive	No GLP, no reference to TG	Tail moment (mean ± SEM): *Blood cells* Control: 2.98 ± 1.08 100 mg/kg bw per day: 8.45*** ± 6.43 Liver cells Control: 7.14 ± 3.41 100 mg/kg bw per day: 14.99*** ± 9.09	6 animals per group sex of animals not clear	p. 404

MN, micronucleus; MNE, micronucleated erythrocytes; NCE, normochromatic erythrocytes; PCE, polychromatic erythrocytes; SEM, standard error of the mean

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4.2.2 Receptor-mediated mechanisms

In section 4.4.2 of the IARC monograph 13 studies are reported. The studies including comments of RMS are summarized in Table 4.2-8.

4 studies compared endocrine disrupting activity of glyphosate and glyphosate-based formulations ([redacted] 2009, ASB2009-7384; [redacted] 2005, ASB2009-9024; [redacted] 2007, ASB2009-9018 and [redacted] 2000, ASB2012-12046). The results demonstrate that glyphosate-based formulations have a higher sex hormone disrupting activity than the active substance glyphosate.

Other studies used only a formulation. Based on the results no conclusion on the active substance is possible.

2 studies investigated endocrine disrupting potential of pesticides in general and did not report results on glyphosate.

Based on the study of [redacted] (2013, ASB2013-11991) it was concluded that proliferative effects of glyphosate on T4/D cells would be mediated by oestrogen receptors. However the results of all animal studies and of epidemiological studies demonstrated that glyphosate and glyphosate-based formulations did not cause breast cancer in animals and humans.

Glyphosate was included into the U.S. EPA Endocrine Disruptor Screening Program's (EDSP). [redacted] (2012, ASB2014-9609) published a short summary of the results. They concluded that, based on the Tier 1 assays that had been performed at different independent laboratories and taking into account the 'higher tier' regulatory safety studies glyphosate might not be considered an endocrine disrupter. Later on, [redacted] (2013, ASB2013-3464) summarized results of the male and female pubertal assays in which glyphosate did not exhibit evidence of endocrine disruption.

Table 4.2-8: Discussion of studies in section 4.2.2 Receptor mediated mechanisms of the IARC monograph

Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 2013, ASB2013-11991	Glyphosate effects on human breast cell cancer growth	The findings suggested that the proliferative effects of glyphosate on T4/D cells are mediated by oestrogen receptors.	Agreement with the reported results.	Yes, page 672	It must be emphasised that no increase in mammary tumours was reported in any of the numerous long-term studies in rats or mice and no increased risk of mammary tumours was found in the epidemiological studies.
[redacted] 2009, ASB2009-7384	Toxicity and endocrine disrupting activity of glyphosate in human cell lines	In human hepatocarcinoma HepG2 cells, four glyphosate-based formulations had a marked effect on the activity and transcription of aromatase, while glyphosate alone differed from controls, but not significantly so. Additionally, although four glyphosate-based formulations dramatically reduced the transcription of ERα and ERβ in ERE-transfected HepG2 cells, glyphosate alone had no significant effect. A stronger effect of the formulations was also reported for the effects on androgen-receptor transcription in a breast cell line.	Agreement with the reported results. The study confirms the clearly higher activity of formulations than of the active substance alone.	Yes, page 671, 686	The study confirms the higher activity of formulations (Roundup) than of the active substance alone. This important difference was already highlighted in the first DAR and also in the RAR.
[redacted] 2005, ASB2009-9024	Effects of glyphosate and Roundup on human placental cells and aromatase	A glyphosate-based formulation caused decreased aromatase activity in human placental cells. Glyphosate alone was without effect.	Agreement with the reported results. The authors Richard et al., 2005 conclude that endocrine and toxic effects of Roundup, not just glyphosate, can be observed in	Yes, page 328, 671, 676 and 682	The study confirms the clearly higher activity of formulations (Roundup) than of

ED_001487B_00000719-00071

Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
			mammals.		the active substance alone. This important difference was already highlighted in the first DAR and also in the RAR.
[redacted] 2007, ASB2009-9018	Time- and dose-dependent effects of Roundup on human embryonic and placental cells	Glyphosate, at non-overtly toxic concentrations, decreased aromatase activity in fresh human placental microsomes and transformed human embryonic kidney cells transfected with human aromatase cDNA. A glyphosate-based formulation, at non-overtly toxic concentrations, had the same effect. The formulation was more active at equivalent doses than glyphosate alone.	The study confirms the higher activity of formulations (Roundup) than of the active substance alone.	Yes, pages 671, 678 and 683-684	The study confirms the higher activity of formulations (Roundup) than of the active substance alone. This important difference was already highlighted in the first DAR and also in the RAR.
[redacted] 2004, ASB2010-14389	Estrogen and androgen activities of pesticides	In human androgen receptor and ERα and ERβ reporter gene assays using the Chinese hamster ovary cell line (CHO-K1), glyphosate had neither agonist nor antagonist activity.	Agreement	No	Several of the 200 tested pesticides were found to have endocrine-disrupting potential; however, no activity of glyphosate was reported.
[redacted] 2010, ASB2015-7815	Endocrine disrupting potential of pesticides	In human androgen receptor and ERα and ERβ reporter gene assays using the Chinese hamster ovary cell line (CHO-K1), glyphosate had neither agonist nor antagonist activity.	Agreement	No	Several of the 200 tested pesticides were found to have endocrine-disrupting potential; however, no activity of glyphosate was

ED_001487B_00000719-00072

Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
					reported.
[redacted] 2000, ASB2012-12046	Inhibition of steroidogenesis by roundup	A glyphosate-based formulation markedly reduced progesterone production in mouse leydig cell tumour cells. The inhibition was dose-dependent. The formulation also disrupted steroidgenic acute regulatory protein expression. Glyphosate alone did not affect steroidogenesis.	Agreement	Yes, pages 327, 328, 332, 677, 678	The study confirms the clearly higher activity of formulations (Roundup) than of the active substance alone. No effects of glyphosate alone have been observed. This important difference was already highlighted in the first DAR and also in the RAR.
[redacted] 2012, ASB2012-11621	Effects of glyphosate and further chemicals on steroidogenesis in a novel murine Leydig cell model	Glyphosate had no effect on testosterone production in a novel murine Leydig cell line. Glyphosate did not modulate the effect of recombinant human chorionic gonadotropin.	Agreement	Yes, page 677	No effects of glyphosate on steroidogenesis.
[redacted] 2013, ASB2014-7614	Endocrine disrupting effects of glyphosate and atrazine in snails.	A glyphosate-based formulation reduced levels of testosterone in gonadal tissue of snails and induced degenerative changes in the ovotestis. CYP450 was increased.	Agreement with the reported results. Only a formulation was tested, therefore, no conclusion on the active substance glyphosate alone is possible.	Yes, page 673	Only a formulation was tested, therefore, no conclusion on the active substance glyphosate alone is possible.
[redacted] 2005, ASB2012-12056	Estrogenic activities of herbicides and surfactants	Glyphosate did not increase plasma vittelogenin levels in juvenile rainbow trout.	Agreement	Yes, page 332,	No estrogenic activity of glyphosate
[redacted] 1983, Z31881	Hypolipidaemia and peroxisome proliferation induced by pesticides	Glyphosate had no effect on formation of peroxisomes or the activity of hepatic carnitine acetyltransferase and catalase, and did not	Agreement	No, study published before 2000	Glyphosate does not have peroxisome proliferator activated

ED_001487B_00000719-00073

Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
		cause hypolipidaemia, suggesting that glyphosate does not have peroxisome proliferator activated receptor activity.			receptor activity.
[redacted] 2008, ASB2013-6443	*In vitro* screening for aryl hydrocarbon receptor agonistic activity in 200 pesticides.	Glyphosate was not an agonist for the aryl hydrocarbon receptor in mouse hepatoma Hepa1c17 cells transfected with a reporter plasmid containing copies of dioxin-responsive element.	Agreement	No	No effect of glyphosate
[redacted] 2010, ASB2010-11410	Teratogenic effects of glyphosate-based herbicides by impairing retinoic acid signalling.	Retinoic acid activity in tadpoles exposed to a glyphosate based formulation was measured. Retinoic activity was increased by the formulation, and a retinoic acid antagonist blocked the effect.	The formulation Roundup classic was used in this study. Therefore, no conclusion on the active substance glyphosate alone is possible.	Yes, page 671, 675, 676, 680	The formulation Roundup classic was used in this study. Therefore, no conclusion on the active substance glyphosate alone is possible.

ED_001487B_00000719-00074

4.2.3 Oxidative stress, inflammation, and immunosuppression

4.2.3.1 Oxidative stress

Human cells *in vitro*, data on glyphosate:

[redacted] (2005, ASB2012-11826) investigated effects of pre-incubation of HaCaT with 100 or 200 µM Vit C, Vit E or both for 0, 24 or 48 h on glyphosate cytotoxicity at doses of up to 25 mM for 24 h. IC_{50} for glyphosate alone, pre-incubated with Vit C, Vit E or both in ranges from 20.9 - 23.9 mM, 20.6 - 23.9 mM, 21.6 - 23.6 mM or 19 - 21.3 mM, respectively. No information is available on the purity of the tested substance.

[redacted] (2010, ASB2012-11610) investigated the formation of reactive oxygen species (ROS) after treatment of HaCaT cells at the IC_{50} using 2',7'-dichlorodihydrofluorescein diacetate. Treatment with 50 mM glyphosate (purity 95%) for 30 min resulted in "*overproduction of H_2O_2*" determined as "*a thicker and more intense fluorescent area*". No quantitative estimate is available.

[redacted] (2014, ASB2014-9603) examined the production of ROS in human erythrocytes (without metabolic activation) using dihydrorhodamine 123. Cells were exposed to glyphosate concentrations of 0.01 - 5.0 mM for 1 h. Positive results are observed from 0.25 mM up to the highest tested concentration that induces cytotoxic effects (increase in percent of haemolysis). No information is available on the purity of the tested substance.

[redacted] (2009, ASB2012-11906) investigated possible effects of *in vitro* exposure of glyphosate on oxidative DNA damage and on oxidative stress parameters (total antioxidant capacity and lipid peroxidation) in human lymphocytes with and without metabolic activation. Cells were exposed to concentrations of 0.5 - 580 µg/mL (up to ca. 3.4 mM). Regarding the induction of cytotoxic effects significantly increased early apoptosis and necrosis at the highest tested concentration of 580 µg/mL were observed. In a modified comet assay oxidative DNA damage was observed without metabolic activation only at a concentration of 3.5 µg/mL whereas an obviously more relevant effect was observed with metabolic activation at the highest tested concentration of 580 µg/mL. Both, determinations of total antioxidant capacity (TAC) as well as the lipid oxidation (determination by level of thiobarbituric reactive substances) indicate an increase of oxidative stress with and without metabolic activation at the highest tested concentrations of 580 µg/mL.

[redacted] (2014, ASB2014-7616, ASB2014-9314) evaluated the effect of glyphosate (purity: 95%) on oxidative stress in HepG2 cells with 2',7'dichlorohydrofluorescin diacetate. Treatment of the cells with 900 mg/mL glyphosate for 24 h does not lead to an increase in ROS. Concentrations up to 1000 mg/mL did not affect the cell viability (MTT test).

Human cells *in vitro*, data on AMPA:

[redacted] (2014, ASB2014-9603) examined the production of ROS in human erythrocytes (without metabolic activation) with dihydrorhodamine 123. Cells were exposed to AMPA concentrations of 0.01 - 5.0 mM for 1 h. Positive results are observed from 0.25 mM up to the highest tested concentration that induces cytotoxic effects (increase in percent of haemolysis). No information is available on the purity of the tested substance.

[redacted] (2014, ASB2014-7616) evaluated the effect of AMPA on oxidative stress in HepG2 cells with 2',7'dichlorohydrofluorescin diacetate. AMPA exposure of the only tested concentration of 900 mg/mL for 24 h does not lead to an increase in ROS. Concentrations up to 1000 mg/mL did not affect the cell viability (MTT test). No information is available on the purity of the tested substance.

Human cells *in vitro*, data on formulations containing glyphosate:

[redacted] (2005, ASB2012-11826) investigated effects of pre-incubation of HaCaT with 100 or 200 µM Vit C, Vit E or both for 0, 24 or 48 h on cytotoxicity of a glyphosate-based formulation (containing 21% (p/p) isopropylamine glyphosate salt (170 g/L), 8% (p/p) POEA and 71% (p/p) water and others minor ingredients) at doses of up to 25 mM for 24 h. IC_{50} for Roundup 3 plus® alone, pre-incubated with Vit C, Vit E or both ranged from 17.1 - 18.2 mM, 16.9 - 18.1 mM, 16 - 17.6 mM or 16.7 - 21.8 mM, respectively. The authors inferred a protective effect of vitamin pretreatment indicating that ROS formation might be a mechanism for cytotoxicity of glyphosate-based formulations.

[redacted] (2013, ASB2014-8034) investigated ROS formation after treatment of HaCaT cells with doses of 0.01, 0.025, 0.05 and 0.1 mM of a glyphosate-based formulation (containing glyphosate 41%, polyethoxethyleneamine (POEA) ≅15%) using 2′,7′-dichlorodihydrofluorescein diacetate. An up to 1.9-fold increase in ROS formation was detected when compared to control and antioxidant N-acetylcysteine (NAC) treated HaCaT cells. The effect was comparable with 10 nM 12-otetradecanoyl-phorbol-13-acetate. The positive control of 100 mM H_2O_2 is questionable as peroxide concentration is expected to decrease in cell cultures after 24 h at 37°C. Pretreatment with NAC statistically significantly decreased ROS formation below vehicle control (apparently not pre-treated with NAC). Some cell proliferation occurred upon treatment with Roundup. However, it was statistically significantly increased only at 0.1 mM glyphosate and after 72 h, but not at lower doses or shorter treatment. The proliferative effect at 0.1 mM after 72 h could be statistically significantly decreased by NAC. Cytotoxicity of the glyphosate formulation occurred from 0.5 mM glyphosate on upwards.

[redacted] (2014, ASB2014-7615) examined the impact of a glyphosate-based formulation (glyphosate as isopropylamine salt, 48%) on oxidative stress in HEp-2 cells with 2',7'-dichlorohydrofluorescin diacetate. The exposure of the only tested concentration of 376.4 mg/mL for 24 h leads to an increase in ROS. The tested concentration is equivalent to the determined LC_{50} value for a 24 h-exposure. The exposure of the formulation also increased glutathione and catalase activity whereas glutathione-S-transferase activity and superoxide dismutase activity (SOD) were not affected.

[redacted] (2014, ASB2014-7616) evaluated the effect of a glyphosate-based formulation (74.4% monoammonium salt of N-phosphonomethylglycine) on oxidative stress in HepG2 cells with 2',7'-dichlorohydrofluorescin diacetate. An increase in ROS was observed at the only tested concentration of 40 mg/mL after an exposure of 24 h. The tested concentration is equivalent to the determined LC_{50} value of 41.22 mg/mL for a 24 h-exposure (MTT test).

Non-human mammalian experimental systems, data on glyphosate:

[redacted] (2009b, ASB2012-11550) investigated the effect of glyphosate, dimethoate and zineb administered alone or in combination on defence systems of the liver, kidney, brain and plasma antioxidant. Male Wistar rats, weighing 190 ± 20 g, were randomly divided into nine groups (4/group). Animals of one group were injected intraperitoneally (i.p.) with 10 mg glyphosate/kg bw (purity: commercial grade) in polyethylene-glycol 400 (PEG-400) three times a week for five weeks. Two groups served as controls (one group without treatment and one group receiving i.p. injections of PEG-400. Six further test groups were used to examine either zineb or dimethoate or a mixture of glyphosate, dimethoate and zineb (these groups are not further discussed here). At the end of the treatment the animals were killed, blood was collected and plasma was prepared. Homogenates from brains, livers, and kidneys were prepared. Various biomarkers of oxidative stress and cell damage were measured. Lipid peroxidation was assessed as thiobarbituric acid-reactive substances (TBARS); the sum of nitrates and nitrites ([NOx]) was measured as the main end-metabolite products of nitric oxide (NO) and peroxinitrite anion ($ONOO^-$), protein carbonyls as a biomarker of oxidative damage to proteins; enzymatic and non-enzymatic biomarkers of the antioxidant defence system: Ferric Reducing Ability of Plasma assay (FRAP, total antioxidant ability in plasma, Vitamin E (α-Tocopherol) levels in liver and brain), total glutathione (GSH) in plasma and brain; catalase activity (CAT), superoxide dismutase activity (SOD), glutathione peroxidase (GPx) activity, glutathione-S-transferase (GST), glutathione reductase (GR) activity in liver, brain, and kidney; lactate

dehydrogenase (LDH) in plasma as a biomarker of cellular damage, and γ-glutamyl transpeptidase (γ–GT) activities as a biomarker of hepato-cellular damage. Results: At the end of treatment with glyphosate no effects were observed on animal behaviour, body weight or body weight gain. Also no clinical signs of toxicity or observations of tremors or gait abnormalities (open field) were observed during the entire experimental period. The analytical examinations showed the following results: Increase of lipid peroxidation in liver, brain, kidney, plasma (significant, $p < 0.01$); slight increase (not significant) of oxidative damage to proteins seen as protein carbonyls in plasma; increase of [NOx] concentration (significant, $p < 0.01$) in brain and plasma; lower values (significant, $p < 0.01$) of FRAP in plasma, liver kidney and brain; progressive loss (significant, $p < 0.01$, approx. 30%) of α-tocopherol in liver and brain; increase (significant, $p < 0.01$) of GSH (GSH and GSSG, glutathione disulphide, oxidized Glutathione, hydrogen acceptor) in plasma; the following values were determined for the various antioxidant enzyme activities: increase (significant, $p < 0.01$) of SOD in liver and brain, decrease (significant, $p < 0.01$) of CAT in brain, slight increase (not significant) of SOD, CAT, GPx, GR, GST activity in kidney; no effect of LDH in plasma, increase (significant, $p < 0.01$) of γ–GT in plasma. Overall, repeated i.p. injection of glyphosate over a period of 5 weeks resulted in a lower antioxidant status in liver, brain, kidney and plasma, higher oxidized protein and glutathione levels in plasma with a decreased concentration of α-tocopherol in brain and liver. SOD was decreased in liver and brain. Glutathione reductase was inhibited in liver while glutathione peroxidase and transferase were unaffected. Plasma lactate dehydrogenase was not affected, but γ-glutamyl transpeptidase activity was increased. In conclusion the IARC statement can be supported that there are indications of oxidative stress in the blood plasma, liver, brain and kidney of rats upon exposure to glyphosate.

[redacted] (1997, Z59299) examined the genotoxic activity of glyphosate and its technical formulation 'Roundup'. Glyphosate (purity: 99.9%) was tested in a battery of genotoxicity tests *in vitro* and *in vivo*. These data were documented as part of the summarized data on *in vitro* and *in vivo* genotoxicity testing with glyphosate in section 4.2.1 of IARC Monographs Volume 112 (2015, ASB2015-8421). No information regarding 'increased biomarkers of oxidative stress in liver and kidney' is given.

Non-human mammalian experimental systems, data on AMPA:

No data available.

Non-human mammalian experimental systems, data on formulations containing glyphosate:

[redacted] (1997, Z59299) examined the genotoxic activity of glyphosate and its technical formulation 'Roundup'. Roundup formulate (30.4% glyphosate as active agent) was tested in a battery of genotoxicity tests *in vitro* and *in vivo*. No information regarding 'increased biomarkers of oxidative stress in liver and kidney' is given. As mentioned above this study was disregarded in the assessment.

[redacted] (2011, ASB2012-11588) evaluated the protective effect of Ginkgo biloba L. leaf extract against Roundup® (Roundup Ultra-Max, containing 450 g/L glyphosate as active ingredient) in Swiss albino mice. Male Swiss albino mice (12 - 14 weeks old and weighing 25 - 30 g) were randomly divided into six groups, each consisting of six animals. The control animals received single intraperitoneal (i.p.) injection with dimethyl sulfoxide (0.2 mL). One group received single i.p. injection of 50 mg/kg bw Roundup. Two further groups were given orally G. biloba at doses of, respectively, 50 and 150 mg/kg bw for 8 consecutive days. The fifth group was given orally G. biloba at the dose of 50 mg/kg bw and i.p. injection of 50 mg/kg bw Roundup. The sixth group was given orally G. biloba at the dose of 150 mg/kg of body weight and i.p. injection with 50 mg/kg bw Roundup. For the fifth and sixth group, G. biloba application was started 5 days before exposure to Roundup and was continued alone for 3 consecutive days after single-dose applications of Roundup. Animals were sacrificed at the end of treatment (72 h). Blood, bone marrow, and liver and kidney tissues were investigated. Serum analysis involved the following parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine. For the determination of lipid peroxidation and glutathione activity the liver and kidney tissues of each animal were processed for biochemical measurements. Tissue glutathione (GSH) and

malondialdehyde (MDA) levels were measured. For evaluation of genotoxic effects the mouse erythrocyte micronucleus (MN) assay, a modified mouse MN test that conventionally scores the MN frequencies in bone marrow polychromatic erythrocytes, was used. For determination of chromosomal aberrations (CAs) animals were sacrificed 2 h after treatment under ether anesthesia and bone marrow from the femur was aspirated, washed, fixed in Carnoy's fixative, and stained with 5% Grünwald–Giemsa stain. Histopathological examination of the liver and kidneys was performed. Results of Roundup treatment without pre-treatment with the antioxidant: Serum AST, ALT, BUN, and creatinine levels were significantly increased ($p < 0.05$) in mice. The examination of the lipid peroxidation products showed significantly decreased ($p < 0.05$) levels of GSH and significantly increased ($p < 0.05$) levels of MDA in the liver and kidney tissues. The frequency of micronucleated cells was clearly increased (significant, $p < 0.05$) in mature normachromatic erythrocytes, and the mean number of micronucleated cells was significantly higher ($p < 0.05$) compared to controls. Roundup induced an increase in the frequency of CAs and the number of AMNs in bone marrow metaphases. It also significantly decreased the rate of MI. A significant stimulation in the frequency of CA types such as chromatid breaks, acentric fragments, and chromatid gaps in bone marrow cells was noted. Histopathology of the liver revealed severe degenerative and necrotic changes. There were hydropic degeneration, nuclear pyknosis, and loss of some nuclei of hepatocytes in periacinar and midsonal areas. Kupffer cell proliferation and fibrosis were seen in some portal areas. In the kidneys glomerular basement membranes were thickened, accumulation of hyaline droplets and cylinders was detected in some tubular lumina, and some tubular epithelial cells were degenerated.

Results of Roundup treatment with pre-treatment with the antioxidant: The treatment of Roundup together with G. biloba caused a significant reduction in the above described effects of Roundup, especially in indices of hepatotoxicity, nephrotoxicity, lipid peroxidation, and genotoxicity. The strongest effect was observed with G. biloba at 150 mg/kg bw.

Overall, results of serum analysis, evaluation of genotoxic effects and the histopathology indicate that Roundup induced (cyto-)toxicity in liver and kidney, higher frequencies of CAs, MNs, and abnormal metaphases compared with the controls, and oxidative stress in Swiss albino mice. The pre-treatment with G. biloba induced a weakening of oxidative stress by the glyphosate-based formulation. The IARC statement can be supported that there are indications of increases in biomarkers of oxidative stress in liver and kidney of mice upon exposure to the glyphosate-based formulation (Roundup). The supplementation with the antioxidant G. biloba extract can protect against glyphosate toxicity by reduction effects of free radicals.

[redacted] (2012, ASB2014-9583) investigated biochemical, hematological and oxidative parameters of glyphosate-Roundup® (= 41% Glyphosate as active ingredient and 16% polyoxyethylene amine (POEA) and apparently other surfactants (not further specified)). Male and female Swiss albino rats (10/sex/dose) received daily oral gavage doses of 50 or 500 mg/kg bw/d Roundup for 15 days (vehicle/control: distilled water). Liver toxicity was assessed by serum enzymes ALT, AST, and γ-GT, renal toxicity assessed by urea and creatinine. Haematology was assessed by RBC, WBC, hemoglobin, hematocrit, MCV, MCH, and MCHC. Oxidative damage assessed by TBARS (thiobarbituric acid reactive substances) and NPSH (non-protein thiols) in liver. There was a significant dose-dependent reduction in body weight gain in both sexes. Significant increases in ALT, AST, and γ-GT at both dose levels, no considerable differences by histology. No significant changes in renal parameters. Hematology: Significant anemic alterations at high dose in both sexes: Reduction of RBC, hematocrit, and hemoglobin, significant increase of MCV. Lipid peroxidation: Males: at both dose levels important increases in lipid peroxidation together with an NPSH reduction in the hepatic tissue. Females: Significant increase in TBARS at both doses, significant decreases in NPSH only at high dose. Results indicate that glyphosate-Roundup® causes anemic effects and increased activities of liver enzymes that indicate liver cell dysfunction (although no abnormal morphology was observed) at subacute exposure and which could be related to the induction of reactive oxygen species.

[redacted] (2014, ASB2014-3919) investigated rat hippocampus. The herbicide Roundup Original® (Homologation number 00898793) containing glyphosate 360 g/L (commercial formulation registered in the Brazilian Ministry of Agriculture) was used, no further information on components are given. Wistar rats were exposed to 1% Roundup in drinking water during pregnancy up to lactation day 15 and from their pups, slices of hippocampus were prepared. TBARS assay was used to assess oxidation

products, reduced GSH was measured with DTNB (both photometric assays). The experimental procedure is in part unclear: "*After preincubation, hippocampal slices were incubated in the presence or absence of 0.01% Roundup for 30 min*", but values are reported as being from 8 animals from each treated group. TBARS levels were statistically significantly increased, ($p < 0.05$), GSH levels were statistically significantly decreased ($p < 0.01$). Remarks: It appears that the results might be a combination of *ex vivo* and *in vivo* results. Positive control is lacking, experimental details are missing. Unusual test setting, the reliability of the test system seems to be questionable. Uncertainties on the test method remain as a preparation of tissue slices was reported, but on the other hand, a homogenate was described. It is unknown whether a homogenate from slices was prepared and tested. Conclusion: From the poor description/questions arising from experimental procedure and due to lack of positive control, this study should be disregarded.

[redacted] (2010, ASB2012-11829) investigated both, carcinogenicity and the change of expression of proteins by proteomics in skin of mice dermally treated with a glyphosate formulation (Roundup original®). Only the proteomics part is assessed here as it relates to oxidative stress. Method: Four male Swiss albino mice were treated each with a single dose of 50 mg/kg bw of glyphosate in a glyphosate formulation (Roundup original®, glyphosate 41%, POEA = 15%-Monsanto Company, St. Louis, MO, USA, 360 g/L glyphosate) by topical application at the dorsal region (2 cm^2, hair clipped). Untreated controls were included. After 24 h animals were sacrificed and skin tissues from the treatment site were excised and homogenized. Protein spots with a >2 fold change (compared to controls) were considered as differentially expressed, excised and identified via MALDI-TOF/TOF. To confirm the observed changes in protein expression an immunoblot analysis for some of the differently expressed proteins was performed. Results: Changes in expression levels of proteins in skin tissues of treated mice compared to controls, which were confirmed by immunoblot analysis, were observed for the three proteins calcyclin (increased expression, about 2.5 fold change), calgranulin-B (increased expression, about 9.5 fold change) and superoxide dismutase (SOD) (decreased expression, about 5 fold change). SOD is a biomarker of oxidative stress and provides a protective response against ROS. The expression of SOD is supposed to be up-regulated if ROS occur. As a down-regulation of SOD was observed it can be concluded that no direct induction of ROS occurred upon treatment with the glyphosate formulation. Calcyclin and calgranulin-B are not directly linked to ROS or oxidative stress. Calgranulin-B is a protein supposed to be involved in chronic inflammation and calcyclin is a calcium-binding protein often detected up-regulated in expression in proliferating cells. Remarks: Only results of the proteomics experiment confirmed by immunoblot analysis were considered as true changes in protein expression levels as only a small number of animals (4), skin samples and one dose were tested. Moreover, the gels were stained with the semi-quantitative silver staining and the detailed procedure of data analysis was not shown (including the total number of gels performed, the expression data of each protein spot on each gel, the significance value for each observed fold change in expression level of a protein spot compared to controls and the group formation for statistical analysis).

Overall, the conclusions drawn by [redacted] (2010, ASB2012-11829) do not support the statement in the IARC report. The study was performed with a glyphosate formulation and not with pure glyphosate as described in the IARC report. No production of free radicals or oxidative stress after dermal exposure to a glyphosate formulation has been observed. An alteration of the expression level of an antioxidant enzyme was found (expression of SOD was down-regulated) but the observed down-regulation of SOD is not indicative of increased ROS formation. Conclusion: The IARC statement that glyphosate increases biomarkers of oxidative stress in skin based on the study of [redacted] (2010, ASB2012-11829) cannot be supported.

Non-human mammalian experimental systems, data on mixtures of active substances including glyphosate:

[redacted] (2013, ASB2014-7493) treated male Wistar rats with a mixture of Zineb (99% pure, 15 mg/kg/d), glyphosate (99% pure, 10 mg/kg/d) and dimethoate (98% pure, 15 mg/kg/d) i.p., 5 x per week for 5 weeks to investigate the association between oxidative stress and

inflammation/steroidogenesis. After treatment period, plasma was sampled and testis homogenates were prepared. For determination of oxidative damage, TBARS and protein carbonyls were determined. Further, the sum of nitrates and nitrites was determined. Statistical analysis was performed. Compared to untreated controls, levels of all biomarkers of oxidative damage were significantly increased in plasma and testis homogenate. No positive control for oxidative stress was included. As glyphosate was only tested in combination with two other pesticides, no conclusion on glyphosate is possible. The IARC text is in principle correct but a more careful wording on the relevance of the study appears appropriate.

Overall conclusion on Oxidative stress:

In general the documentation of the majority of studies on oxidative stress in section 4.2.3 of IARC Monographs Volume 112 (2015, ASB2015-8421) can be confirmed. It is noted that here is a lack of positive controls for oxidative stress in all *in vitro* and *in vivo* studies described in section 4.2.3 *(ii) Non-human mammalian experimental systems* of the IARC monograph. From the available data on glyphosate, there is some indication of induction of oxidative stress from testing in human cell cultures and in mammalian (*in vivo*) experimental systems. In particular, the IARC statement that there are indications of oxidative stress in the blood plasma, liver, brain and kidney of rats upon exposure to glyphosate can be supported. However, only one of the cited studies ([redacted] 2009b, ASB2012-11550) investigated oxidative stress in animals with pure glyphosate. This study was conducted in rats and no other species was tested and increased oxidative stress was observed in combination with cytotoxic/degenerative effects of the targeted organs.

Only *in vitro* data were available on induction of oxidative stress by AMPA. There was no indication for such activity.

A glyphosate-based formulation increased biomarkers of oxidative stress in livers and kidneys of mice treated orally for 1 day or 15 days.

Considering the low level of metabolism and the chemical structure of glyphosate, glyphosate radical formation initiating oxidative stress appears unlikely. However, uncoupling or inhibition of mitochondrial oxidative phosphorylation also represents an established mechanism for ROS generation. Notably, uncoupling of oxidative phosphorylation by glyphosate has been reported in rat liver microsomes ([redacted] 1979, ASB2015-8535) and a glyphosate formulation (but not glyphosate) ([redacted] 2005, ASB2012-11994).

Induction of oxidative stress, in general, can provide a mechanistic explanation for any observed cytotoxic/degenerative and indirectly genotoxic effects of substances (Chapter 3.6.2.3.2 Additional considerations for classification of Guidance on the Application of the CLP criteria, ECHA-13-G-10-EN, ECHA 2013, ASB2015-8592). However, from the sole observation of oxidative stress and the existence of a plausible mechanism for induction of oxidative stress through uncoupling of mitochondrial oxidative phosphorylation alone, genotoxic or carcinogenic activity in humans cannot be deduced for glyphosate and glyphosate based formulations.

4.2.3.2 Inflammation and immunomodulation

Six studies were reported by IARC in section 4.2.3 (b). The studies including comments of the RMS are summarized in Table 4.2-9 and are described in detail below.

(i) Humans:

Human cells *in vitro*:

Data on glyphosate:

[redacted] (2002, ASB2012-11919) tested the proliferative activity and the release of cytokines

of 1-1000 µM glyphosate on PHA-stimulated human peripheral blood mononuclear cells (PBMC) of unknown origin.

After 24 h incubation, glyphosate had a slight (not significant) inhibitory effect on cell proliferation, INF-y was significantly reduced at 1000 µM glyphosate (-30%) and a minimal reduction of IL-2 was recorded. No effects on TNF-alpha or IL-1 beta. The authors concluded glyphosate showed only a little damage to the immune system.

Remarks: The study of [redacted] (2002, ASB2012-11919) is limited due to the Japanese language. Only a summary and some figures with labelling in English is available, lack of information on the test method, numerical results and the details on the cell donator. The *in vitro* finding (reduction in INF-Y) is opposite to the *in vivo* response in BAL (increase in INF-y) seen in [redacted] (2014, ASB2015-8276). The relevance of this study seems to be questionable. The highest test concentration of 1 mM that inhibited cell proliferation may be close to a cytotoxic concentration (no data).

Most of the information was correctly cited by IARC. The reported finding 'modestly inhibited the production of IFN-gamma' can be accepted for IFN-gamma (-30%), but no clear effect was seen for IL-2 up to 1000 µM glyphosate.

(ii) Non-human mammalian experimental systems:

Data on glyphosate:

The study of [redacted] (2014, ASB2015-8276) used the 'murine intranasal challenge model' with daily intranasal applications for 7 days or 3x/week for 3 weeks of glyphosate-rich air samples (called as 'Real Env.') suspended in PBS (8.66 µg/mL) or reagent grade glyphosate (of unknown purity) at concentrations 100 ng, 1 µg or 100 µg in 30 µl in wild-type of TLR 4-/- mice. (Cell numbers by flow cytometric analysis on BAL and lung tissue, cytokine levels in BAL, serum, immunohistochemistry in lung tissue).

Increases in numbers of cells, eosinophils, neutrophils per lung or BAL fluid at 1 µg and 100 µg glyphosate, but no dose-response was observed. No effect occurred at 100 ng glyphosate. No increase in mast cell number/lung tissue, but higher serum MCPT-1 indicating increased mast cell degranulation was found.

1 or 100 µg glyphosate induced increased release of cytokines (IL-5, Il-10, IL-13 without dose-response for IL-5 and IL-13) to BAL fluid. Although no dose response was recognized, IFN-Y was increased nasal application of glyphosate at both dose levels. In contrast the increase was not confirmed for the 'Real Env.' exposure. IL-4 was increased for 'Real Env.' but not for glyphosate.

At 1 µg glyphosate, 3-4-fold higher levels of IL-33 and TSLP in BAL and (a qualitative) confirmation by positively immuno-stained (bronchiolar?) lung tissue was reported.

Remarks: The study aimed to identify the potential of glyphosate to induce asthma. To our knowledge there are no validated models to assess the potential for respiratory sensitization.

The validity of the administration route and frequency is limited to assess effects after repeated inhalation. Due to the single intranasal injection of the test fluid there is lack of homogenous concentration and lack of constant exposure conditions over 6 hour per day. This method did not produce a continuously homogeneous test atmosphere at the mucosal surface of the airways. As the test material concentrations will be highest in the nasal cavity, the nasal tissues are the preferred sites for cytokine and morphological examinations. In addition, it remains unclear how many animals/sex/dose were treated and how many samples of BAL and lung tissue per animals were examined.

More weight should be given on the testing of glyphosate. Testing of the glyphosate-rich air samples are considered as less informative as the analytical concentration, composition, homogeneity and stability of the air samples were not examined. In comparison with the sham-(PBS) exposed mice the study identified an increase of biomarkers of airway inflammation as shown by increased numbers of

cells and increased numbers of inflammatory cells (eosinophils, neutrophils) and elevated cytokine concentrations in BAL. The positive response could be interpreted as qualitative information indicating a potential for airway inflammation since for the majority of cell parameters and cytokines no dose-response was identified. The absence of a dose-response relationship might have been related to the application mode. Increased levels of IL-33 and TSLP in BAL and abundant staining in lung tissue were interpreted as indicative of (asthma-like) type 2 pathology. These effects as well as increased concentrations of released cytokines that are related to asthma (IL-5, IL-10, IL-13) and mast cell degranulation were also seen following ovalbumin administration with a similar dosing scheme. The authors interpreted the results as indicating that glyphosate triggers allergic inflammation. As there is no validated model on respiratory sensitization and due to the weaknesses of the study, this conclusion needs confirmation by other studies or human data.

The study results were (almost) correctly reported by IARC. In contrast to the IARC text, no effect was seen at 1 ng glyphosate.

In the study of [redacted] (1992, TOX9551954) Groups of 10 male and 10 female F344N rats and B6C3F1 mice were given glyphosate in feed at dietary concentrations of 0, 3125, 6250, 12500, 25000 or 50000 ppm (corresponding to 0, 205, 410, 811, 1678 or 3393 mg/kg for males rats and 0, 213, 421, 844, 1690 or 2293 mg/kg bw/d for female rats). Ten additional rats/sex were included at each dietary level for evaluation of hematologic and clinical pathology parameters (on days 5, and 21, and at the end of treatment after 13 weeks).

In male rats, reduced body weight (bw) gains were observed in the 25000 and 50000 ppm groups. The final bw in these groups were significantly lower than that of the control group. At necropsy the bw of the 50000 ppm male group was 18% less than that of controls. In female rats of this dose there was only a marginal effect on bw gain with the high dose group 5% lighter than controls at the end of study. In male rats of this dose, small increases in relative organ weight were observed for the liver, kidney, and testicle; a decrease in absolute weight and relative weight was observed for the thymus. The relative weight was 0.80% for high dose males versus 0.92% in control males. No treatment-related effects in females and on food consumption were observed.

Mild increases in haematocrit and RBC were observed in male rats at 13 weeks at ≥12500 ppm and increased haemoglobin in male rats at ≥25000 ppm. In female rats, minimal but significant increases occurred in lymphocyte and platelet counts, WBC, MCH and MCV. Treatment-related alterations in clinical chemistry parameters included increases in alkaline phosphatases in males and females at all-time points, ALAT in males and females at all-time points except 90 days, total bile acid at days 23 and 90 in males and at day 23 in females, total protein in females at all-time points, and sporadic increases in urea nitrogen and albumin.

In the 13-week study in mice, significantly lower final bw, lower relative thymus weights and increased relative weights of liver, heart, testes, lungs and kidneys were seen in high dose male mice, significantly lower final bw and lower absolute thymus and liver weights were observed in high dose female mice. A dose-related cytoplasmatic alteration of the parotid salivary gland in male mice and female mice at all doses (except the low dose) were seen. No data on haematology and clinical chemistry were available.

Remarks: The 13-week studies were conducted in 1988; the used method is not comparable to the current OECD test guideline standard. Increased haematocrit and RBC may indicate a lower water consumption and dehydration status of the animals (no data on water consumption available). Elevated ALAT and total bile acids could be related to hepatobiliary dysfunctions (in the absence of histopathological findings reported). Lower absolute and relative thymus weight alone in high dose males without any corresponding (microscopic) effect on immune organs or immune compartments in other tissues is not sufficient to indicate an immunosuppressive effect of glyphosate. More likely it could be interpreted as a nonspecific (toxic) response together with a lower bw gain that resulted in 18% lower final bw at 50000 ppm. Based on the limited information available it can be concluded that the observations in rats are in agreement with the findings in mice.

To the IARC Documentation:

IARC summed up the main findings as 'pathological effects of glyphosate on the immune system'

without giving an interpretation of the effects seen. Based on a weight of evidence analysis of the available data from the studies in rats and mice one should conclude that there is no clear indication of an immunosuppressive effect.

Glyphosate-based formulation:

In the study of [redacted] (1997, ASB2015-7878) female CD-1 mice received drinking water for 26 days at concentrations from 0, 0.35%, 0.7% or 1.05% Roundup (corresponding to 0, 335, 670 or 1000 mg/kg glyphosate/ kg/day. On day 21 mice were i.p. injected with sheep red blood cells (SRBC) and the production of the T-lymphocyte, macrophage dependent antibody response was evaluated on day 26.

No treatment-related effect on bw gain or water consumption. Roundup did not affect the T-cell mediated antibody production.

Remarks: There is no indication that the humoral immune response is adversely affected in mice that received Roundup for 26 days of treatment.

IARC correctly summed up the study results. The lack of effects on the immune system has not been reflected in their overall conclusion.

Overall conclusion on section (b) inflammation and immunomodulation:

IARC documented the results of one *in vitro* and three *in vivo* studies that examined for glyphosate-related effects on the mammalian immune system in this section.

With regards to the underlying mode of action for the carcinogenic effects IARC concluded that there is 'weak evidence that glyphosate may affect the immune system, both the humoral and cellular response' (section 5.4).

RMS concludes that the evidence from available data do not allow to conclude that glyphosate caused immunosuppression. However it is to note that due to the small number of studies assessed and the fact than all studies show limitations, no robust information is available to conclude on the immunomodulatory action of glyphosate.

Conclusion on glyphosate:

The main study results of the above mentioned studies were correctly summed up by IARC. Some details of the reporting could be improved. In the study of [redacted] (2014, ASB2015-8276) no effect was seen at the low dose tested (100 ng glyphosate) in mice. A critical analysis of the limitations of the studies (e.g. on the exposure regimen) is lacking.

The effects of the 13-week study in rats ([redacted] 1992, TOX9551954) were described by IARC as 'pathological effects of glyphosate on the immune system'. The only finding was a reduced absolute/relative thymus weight in male rats at the highest dose. No other corroborating effect in the immune organs was seen. The lower weight of the thymus is likely to be linked to nonspecific toxic effects such as a lower bw gain and a 18% lower final bw in male rats. No such effect was seen in female rats of this study. No clear pathological (immune suppressive) effect on the immune system can be identified from this study.

The study of [redacted] (2014, ASB2015-8276) indicated that glyphosate may induce inflammatory effects in the respiratory tract that by the authors was supposed as being predictive to induce asthma-like effects. Additional and more robust data are needed to confirm this assumption. A potential for inflammatory responses of the respiratory tract is the only immunomodulatory effect identified so far.

Conclusion on glyphosate-containing formulation (Roundup):

The negative results for glyphosate of the [redacted] (1992, TOX9551954) are in agreement with the negative finding for effects on the immune system of the study of [redacted] (1997, ASB2015-7878). Although both studies had limitations (in comparison to current test guideline standards or the test material), the negative outcome was not reflected by IARC. The glyphosate-containing formulation tested in the [redacted] (1997, ASB2015-7878) was negative for T-cell dependent antibody response up to 1000 mg/kg bw/d glyphosate and did not indicate that the humoral and cellular immune responses were affected.

Table 4.2-9: Discussion of studies in chapter 4.2.3 (b) Inflammation and immunomodulation of the IARC monograph

Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
[redacted] 2002, ASB2012-11919	Effects of glyphosate on cytokines production by human peripheral blood mononuclear cells	Glyphosate had a slight inhibitory effect on cell proliferation, and modestly inhibited the production of IFN-gamma and IL_2. The production of TNF-alpha and IL-1 Beta was not affected by glyphosate.	Agreement. The authors conclude that glyphosate might be a pesticide with only a little damage to the immune system. The study of [redacted] (2002) is limited due to the Japanese language. Only a summary and some figures with labelling in English is available, lack of information on the test method, numerical results and the details on the cell donator. The *in vitro* finding (reduction in INF-Y) is opposite to the *in vivo* response in BAL (increase in INF-y) seen in [redacted] 2014, ASB2015-8276. The relevance of this study seems to be questionable. The highest test concentration of 1 mM that inhibited cell proliferation may be close to a cytotoxic concentration (no data).	No	The relevance of this study seems to be questionable.
[redacted] 2014, ASB2015-8276	Pro-inflammatory effects of glyphosate and farm air samples in mice	Airway exposure to glyphosate significantly increased the total cell count, eosinophils, neutrophils, and IgG1 and IfG2a levels and produced pulmonary inflammation. Glyphosate-rich farm air increased circulating levels of IL-5, IL-10, IL-13 and IL-14 in wildtype and TLR4-/- mice. In wildtype mice glyphosate increased levels of IL-5, IL-10, IL-13 and IFN-Gamma (but not IL-4).	Agreement with reported results. The study aimed to identify the potential of glyphosate to induce asthma. The positive response could be interpreted as qualitative information indicating a potential for airway inflammation since for the majority of cell parameters and cytokines no dose-response was identified. Testing of the glyphosate-rich air samples are considered as less informative as the	No	Agreement with reported results; the positive response could be interpreted as qualitative information indicating a potential for airway inflammation.

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Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
			analytical concentration, composition, homogeneity and stability of the air samples were not examined.		
[redacted] 1992, TOX9551954	NTP report on toxicity studies of glyphosate in mice	In subchronic studies in rats and mice effects on thymus weight and haematological parameters have been observed.	Further effects on clinical chemistry parameters, body weight and salivary gland have been reported. The 13-week studies were conducted in 1988; the used method is not comparable to the current OECD test guideline standard. The results are not sufficient to indicate an immunosuppressive effect of glyphosate. More likely they could be interpreted as a nonspecific (toxic) response together with a lower bw gain that resulted in 18% lower final bw at 50000 ppm.	Yes, page 259	Supplementary information on subchronic toxicity of glyphosate in rats and mice additionally to the large number of studies reported in the RAR; The results are not sufficient to indicate an immunosuppressive effect of glyphosate. More likely they could be interpreted as a nonspecific (toxic) response.
[redacted] 1997, ASB2015-7878	Effect of Roundup on antibody production in mice	The humoral immune response (antibody production against sheep erythrocytes) was not affected by glyphosate.	Agreement	No, reported before 2000	No effect of glyphosate on humoral immune response.
[redacted] 2011, ASB2015-8279	Effects of glyphosate on haematological and immunological parameters in catfish	"A positive association between exposure to glyphosate and immunotoxicity in fish has been reported."	No agreement with conclusion of IARC. Obviously, no glyphosate but a glyphosate containing formulation was used in this study. Without further information it is a mixture of unknown substances. Therefore, no conclusion on glyphosate is possible.	Yes, page 147	No agreement with conclusion of IARC. Obviously, no glyphosate but a glyphosate containing formulation was used in this study. Without further

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Study (Author/year)	Subject	Evaluation by IARC	Comment RMS on IARC evaluation	Study reported in RAR Draft April 2015	Final conclusion of RMS, considering IARC evaluation
					information it is a mixture of unknown substances. Therefore, no conclusion on glyphosate is possible.
[redacted] 1998, ASB2015-8422	Effects of glyphosate on the immune response and protein biosynthesis of fish	Effects of a glyphosate-based formulation on immune response in bolti fish are reported.	Some effects are described by IARC as glyphosate effects. However, a formulation was used in this study. Therefore, no conclusion on the active substance glyphosate is possible.	No, reported before 2000	Some effects are described by IARC as glyphosate effects. However, a formulation was used in this study. Therefore, no conclusion on the active substance glyphosate is possible.

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4.2.4 Cell proliferation and death

Information on apoptosis and proliferation in neuroprogenitor cells from humans (ReN CX) and mice (mCNS) is available from a HTS assay reported (refer to section 4.3).

4.3 Data relevant to comparisons across agents and end-points

IARC stated that no HTS or other relevant data was available to its working group. This included any data from Tox21 or the ToxCast initiatives.

In the RAR (April 2015, ASB2015-1194) information on androgenic and estrogenic effects from the U.S. EPA Endocrine Disruptor Screening Programme are reported. Based on Tier 1 studies of this programme as well as results published as part of the OECD validation of the steroidogenesis assay, and taking into account higher tier regulatory safety studies, it was concluded that there is no evidence for effects on the androgenic or estrogenic pathways of the endocrine system (refer to section 4.2.2).

In addition, the RAR contained information from a HTS assay for apoptosis and proliferation in neuroprogenitor cells from humans (ReN CX) and mice (mCNS). Glyphosate did not activate proliferation (BrdU assay) or apoptosis (caspase 3, p53 pathways) in concentrations between 0.001 and 100 µM in these tests.

DNA microarray data is available for Japanese medaka treated with 16 mg/L glyphosate or its mixture with 0.5 mg/L surfactant for 48 h ([redacted] 2012, ASB2015-8590). None of 138 genes that were induced in the liver by the treatment with the combination was associated with mutagenesis or carcinogenesis. Glyphosate alone did not lead to significant hepatic gene expression changes in this fish.

4.4 Cancer susceptibility data

IARC stated that studies examining relevant susceptibility factors were not identified.

In contrast, the RMS considered Swiss albino mice as a potentially susceptible strain for certain tumours: "*Swiss albino mice with high background prevalence of malignant lymphoma could be more vulnerable than other strains.*" (RAR, April 2015, ASB2015-1194). It was discussed that although it could not be completely excluded that the increase in malignant lymphoma incidence over the historical control of the laboratory reported by [redacted] (2001, ASB2012-11491) was treatment-related, this (potential) effect was "*confined to this single study and strain*".

In its communication entitled "Does glyphosate cause cancer? Preliminary assessment of the carcinogenic risk of glyphosate with regard to the recent IARC evaluation", it was later noted by the BfR: "*Apart from the statistically significant increase in Swiss mice, a higher number of affected top dose males was also seen in two other studies ([redacted] 1997 [22] and [redacted] 2009 [23]) but was contravened later by historical control data.*" (BfR, 2015, ASB2015-8593). The following comparative table was provided:

Table 4.4-1: **Total incidence of malignant lymphoma in long-term studies with glyphosate in different mouse strains (Table reproduced from BfR-communication entitled: "Does glyphosate cause cancer? Preliminary assessment of the carcinogenic risk of glyphosate with regard to the recent IARC evaluation" (BfR, 2015, ASB2015-8593).**

Study, Strain		Males				Females			
[redacted] 2009, ASB2012-11492 Crl:CD-1 (ICR) BR	Dose (ppm)	0	500	1500	5000	0	500	1500	5000
	Affected	0/51	1/51	2/51	5/51	11/51	8/51	10/51	11/51
[redacted] 2001, ASB2012-11491 HsdOLA:MF1 (Swiss albino)	Dose (ppm)	0	100	1000	10000	0	100	1000	10000
	Affected	10/50	15/50	16/50	19/50*	18/50	20/50	19/50	25/50*
[redacted] 1997, ASB2012-11493 Crj:CD-1 (ICR)	Dose (ppm)	0	1600	8000	40000	0	1600	8000	40000
	Affected	2/50	2/50	0/50	6/50	6/50	4/50	8/50	7/50
[redacted] 1993, TOX9552382, CD-1 (not further specified)	Dose (mg/kg bw/d)	0	100	300	1000	0	100	300	1000
	Affected**	4/50	2/50	1/50	6/50	14/50	12/50	9/50	13/50

* increase statistically significant, for females based on percentage and not on total number of affected mice
** based on histological examination of lymph nodes with macroscopic changes

4.5 Other adverse effects

A number of further (adverse) effects observed in humans and laboratory animals were discussed by both IARC and BfR. Respective findings have been taken into account in the chapters above as far as these were considered relevant for the assessment of carcinogenic and/or mutagenic potential.

5 Summary of Data Reported

5.1 Exposure data

Results of four occupational and two para-occupational studies using various glyphosate-containing plant protection products have been cited in the IARC monograph. The studies were carried out between 1988 and 2007 in different countries of North America and Europe. Four of these studies ([redacted] 1988 (ASB2015-7889), [redacted] 1992 (TOX9650912), [redacted] 2005 (ASB2012-11859) and [redacted] 2007 (ASB2012-11597)) have not yet been included in the RAR (April 2015, ASB2015-1194) because a refinement of operator exposure was not necessary.

Within the scope of the risk assessment for the representative formulation in the European procedure for renewal of approval of glyphosate the exposure calculations according to the common models demonstrate safe use of the product.

Nevertheless, all six exposure studies have been roughly evaluated now (see Table A-5.5-2).

In all cases but one, the recorded values in the studies were below or in the same order of magnitude as those predicted in the RAR (April 2015, ASB2015-1194). Thus, it can be stated that there is no glyphosate based health risk anticipated for operators for intended uses applied for in the European Union provided that the plant protection product is used correctly and as intended.

However, in one study ([redacted] 2005, ASB2012-11859) the reported glyphosate air concentrations for some operators (vehicle application) were strikingly high, i.e. higher than the air concentrations detected in all other studies by a factor of 1000. But it is assumed that the data in this study were obtained with invalid calibration. For more details see Table A-5.5-2.

In summary, for resources on dietary exposure and for results on biological markers IARC refers to several selected reports from national food- and bio-monitoring programmes as well as to some studies in the public literature. Most of the data on dietary consumer exposure are not included in the RAR (April 2015, ASB2015-1194) due to the GAP-based "safe-use" approach for the assessment of active substances under Regulation (EU) 1107/2009 (2009, ASB2015-8589). All studies on biomarkers were also included in the RAR. No deviating conclusions between RAR and IARC were identified.

5.2 Human carcinogenicity data

Based on the studies on cancer in humans IARC concluded: „*There is limited evidence in humans for the carcinogenicity of glyphosate.*" RMS agrees with IARC that the other IARC categories (Evidence suggesting lack of carcinogenicity, inadequate evidence of carcinogenicity and sufficient evidence of carcinogenicity) are not suitable for the classification of the evidence from studies in humans. The evaluation of the epidemiological studies by the RMS is similar to IARC. However, RMS adopts a more cautious view since no consistent positive association is observed, with the most powerful study showing no effect. The IARC interpretation is more precautionary based on the objectives and scope of the IARC Monographs which represent a first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans and that the Monographs may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available. Therefore, no recommendation is given with regard to regulation or legislation, which is the responsibility of individual governments or other international organizations.

It was also noted that in the epidemiological studies a differentiation between the effects of glyphosate and the co-formulants is not possible. However, data on glyphosate containing formulations indicate a significantly higher toxicity compared to the pure active substance.

5.3 Animal carcinogenicity data

Based on carcinogenicity studies in experimental animals IARC concluded: „*There is sufficient evidence in animals for the carcinogenicity of glyphosate*" on a positive trend in the incidence of renal neoplasms in male CD-1 mice, a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice and a significant increase in the incidence of pancreatic islet cell adenoma in two studies in the Sprague-Dawley rats.

A much larger number of animal studies have been performed to evaluate the carcinogenic potential of glyphosate than necessary by the legal requirements. In mice, a total of five long-term carcinogenicity studies using dietary administration of glyphosate were considered. In rats, seven chronic toxicity and carcinogenicity studies using dietary administration of glyphosate and two studies with application via drinking-water were reviewed.

In order to support the interpretation and evaluation of the tumour incidences observed in the CD-1 mice studies Table 5.3-1 was prepared (see below).

Renal tumours

In four studies in CD-1 mice and one study in Swiss albino mice, the incidences of renal tumours in male mice were reconsidered for statistical evaluation. In the first study ([redacted] 1983 TOX9552381), the combined incidences for renal adenoma and carcinoma in males were 1, 0, 1 or 3 for the control, low, mid or high dose group, respectively, based on the result of the histopathological re-examination and 0, 0, 1, 3 when based on the original study report. In the second study ([redacted] 1997, ASB2012-11493), the incidences for renal adenoma were 0, 0, 0 or 2 for the control, low, mid or high dose group males, respectively. In Swiss albino mice ([redacted] 2001, ASB2012-11491) reported incidences in males were 0, 0, 1, 2. For these three studies, the statistical analysis with the Cochran-Armitage test for linear trend yielded a significant result, whereas the analysis by pair-wise comparisons (Fisher's exact test) indicated no statistically significant differences between the groups. In the two other studies, as well as the females of all studies, there was no indication for induction of renal adenoma.

For both studies in CD-1 mice, the observed renal tumours were considered spontaneous and unrelated to treatment by the study pathologists. Furthermore, extensive pathological and biometrical re-evaluations of the data from the first study reached the conclusion that the absence of any pre-neoplastic kidney lesion in treated males provided sufficient evidence that the occurrence of these tumours was spontaneous rather than substance-induced ([redacted] 1986, TOX9552381). This assessment is supported by the fact that, in both studies, the increased incidences of renal tumours at the high dose groups were not statistically significant when compared with the concurrent controls, and the incidences were within the historical control range for adenomas and carcinomas combined (up to 6%).

The EU CLP regulation provides further important factors which should be taken into consideration for the interpretation and assessment of animal carcinogenicity data. If increased tumour incidences are found only at the highest doses used in a lifetime study, the possibility of a confounding effect of excessive toxicity cannot be excluded. In both studies, the highest dose levels tested (4841 or 4348 mg/kg bw per day) were well in excess of the limit dose for carcinogenicity testing (1000 mg/kg bw per day) as recommended by OECD guidance document 116 (OECD 2012). Also, the OECD test guideline for carcinogenicity studies states that the highest dose level should elicit signs of minimal toxicity, with depression of body weight gain of less than 10%. In both studies, however, the body weight gain in high dose males was decreased by more than 15% compared to controls, and there was a significant increase in central lobular hepatocyte hypertrophy, central lobular hepatocyte necrosis, and chronic interstitial nephritis in high dose males in one study ([redacted] 1983 TOX9552381).

Table 5.3-1: Summary of selected tumour incidences in male CD-1 mice.

	Historical control incidences			**Tumour incidence/number of animals examined**																
Dose (mg/kg bw per day)	*Mean*	*Min*	*Max*	0	0	0	0	71	100	157	165	234	300	810	814	838	1000	4348	4841
Study ID				A	B	C	D	D	B	A	C	D	B	D	A	C	B	C	A
Study duration (months)	*NR*	*18*	*24*	24	24	18	18	18	24	24	18	18	24	18	24	18	24	18	24
Survival	*NR*	*18.3%*	*94%*	20/50	26/50	26/50	39/51	41/51	25/50	16/50	34/50	39/51	29/50	35/51	17/50	27/50	25/50	29/50	26/50
Renal tumours#	*0.43%*	*3.43%*	*6.0%*	1/49	2/50	0/50	0/51	0/51	2/50	0/49	0/50	0/51	0/50	0/51	1/50	0/50	0/50	2/50	3/50
Malignant lymphoma	*4.09%*	*1.45%*	*21.7%*	2/48	4/50	2/50	0/51	1/51	2/50	5/49	2/50	2/51	1/50	5/51	4/50	0/50	6/50	6/50	2/49
Haemangiosarcoma	*1.13%*	*1.67%*	*12.0%*	0/48	0/50	0/50	0/51	0/51	0/50	0/49	0/50	0/51	0/50	0/51	1/50	0/50	4/50	2/50	0/49

Study ID: A = [redacted] (1983, TOX9552381), re-evaluation; B = [redacted] (1993, TOX9552382); C = [redacted] (1997, ASB2012-11493); D = [redacted] (2009, ASB2012-11492).

Renal tumours: combined incidence of adenoma and carcinoma.

HC: Historical control data for Crl:CD-1 (ICR)BR mice ([redacted] 2000). The data was gathered from 51 studies of at least 78 weeks duration which were initiated between January 1987 and December 1996.

Mean: Mean (in percent of total); Min: Minimum (in percent found); Max: Maximum (in percent found).

NR: Not reported.

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Haemangiosarcoma

In two studies in CD-1 mice, the incidences of haemangiosarcoma in male mice were reconsidered for statistical evaluation. In the first study ([redacted] (1993, TOX9552382), the combined incidences for haemangiosarcoma were 0, 0, 0 or 4 for the control, low, mid or high dose group. In the second study ([redacted] 1997, ASB2012-11493), the incidences for haemangiosarcoma were 0, 0, 0 or 2 for the control, low, mid or high dose group, respectively. For both studies, the statistical analysis with the Cochran-Armitage test for linear trend yielded a significant result, whereas the analysis by pair-wise comparisons (Fisher's exact test) indicated no statistically significant differences between the groups.

The background incidences for haemangiosarcoma in male CD-1 mice provided by Charles River Laboratories (2000; from 51 studies, initiated between 1987 and 1996) were up to 6/50 (12%) if multiple organs were considered, and were up to 5% or 8% in liver and spleen, respectively. Therefore, the conclusion of the study pathologists that the observed incidences for haemangiosarcoma were spontaneous and unrelated to treatment is supported by the RMS.

Pancreatic and other tumours

The statistically significant increase in pancreatic tumours incidences in the male rats of the low dose groups of [redacted] (1981, TOX2000-595, TOX2000-1997) and [redacted] (1990, TOX9300244) are considered incidental. With regard to the positive trend for liver cell adenoma in male rats and thyroid C-cell adenoma in females for the study of [redacted] (1990, TOX9300244), IARC noted lack of evidence for progression.

Malignant lymphoma

IARC did also consider a review article ([redacted] 2015, ASB2015-2287) containing information on five long-term bioassay feeding studies in mice, in which a statistically significant increase in the incidence of malignant lymphoma was reported, but the IARC Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.

In three studies in CD-1 mice, the incidences of malignant lymphoma in male mice were reconsidered for statistical evaluation. For the control, low, mid or high dose group, the respective incidences in the first study were 0, 2, 2 or 5 ([redacted] 2009, ASB2012-11492), in the second study the incidences were 2, 2, 0, 6 ([redacted] 1997, ASB2012-11493), and in the third study the incidences were 4, 2, 1, 6 ([redacted] 1993, TOX9552382). For the first and second study, the statistical analysis with the Cochran-Armitage trend test yielded a significant result, whereas the analysis by pair-wise comparisons (Fisher's exact test) indicated no statistically significant differences between the groups for all three studies.

A study in Swiss albino mice ([redacted] 2001, ASB2012-11491) was also reconsidered for statistical evaluation. The incidences in males were 10, 15, 16 or 19 for the control, low, mid or high dose group, respectively. Neither the Cochran-Armitage trend test nor the pair-wise comparisons using Fisher's exact test yielded a significant result. However, using the Z-test, the pair-wise comparison between the control and high dose group gave a statistically significant result, as reported in the RAR.

For the assessment of the biological significance of these findings, it is important to consider that malignant lymphomas are among the most common spontaneously occurring neoplasms in the mouse. For the CD-1 mouse strain, incidences of up to 13/60 (21.7%) have been reported in male control groups. Thus, the incidences observed in the above studies, with a maximum of 6/50 (12%), were all within the historical control range. Also in the study with Swiss mice, which have considerably higher background incidences for malignant lymphomas, the observed incidences were within the historical control range. Therefore, the conclusion of the study pathologists that the observed malignant lymphomas were spontaneous and unrelated to treatment is supported by the RMS.

For an overall conclusion, the large volume of animal data for glyphosate should be evaluated using a weight of evidence approach. It should be avoided to base any conclusion only on the statistical

significance of an increased tumour incidence identified in a single study, without consideration of the biological significance of the finding.

In summary, based on the data from five carcinogenicity studies in mice and seven chronic toxicity and carcinogenicity studies in rats, the weight of evidence suggests that no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria.

5.4 Mechanistic and other relevant data

Glyphosate has been tested in a broad spectrum of mutagenicity and genotoxicity tests *in vitro* and *in vivo*. Taking into account all available data and using a weight of evidence approach, it is concluded that glyphosate does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria.

AMPA has been tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in an adequate range of assays. Taking into account all available data and using a weight of evidence approach, it is concluded that AMPA does not induce mutations *in vivo* and no hazard classification for mutagenicity is warranted according to the CLP criteria.

Glyphosate-based formulations have been extensively tested for mutagenicity and genotoxicity *in vitro* and *in vivo* in a wide range of assays. However, since formulation compositions are considered proprietary, the specific composition of the formulations tested was not available for the published studies. Positive results from *in vitro* chromosomal damage assays and tests for DNA strand breakage and SCE induction were reported in published studies. Also, for specific glyphosate-based formulations, *in vivo* mammalian chromosomal aberration or micronucleus assays as well as tests for DNA adducts, DNA strand breakage and SCE induction gave positive results in some published studies. However, no regulatory studies for these endpoints were provided. Thus, for the different glyphosate-based formulations, no firm conclusions can be drawn with regard to a need for classification according to the CLP criteria.

In general the documentation of the majority of studies on oxidative stress can be confirmed, but it is noted that there is a lack of positive controls for oxidative stress in all *in vitro* and *in vivo* studies described in the IARC monograph. From the available data on glyphosate, there is some indication of induction of oxidative stress from testing in human cell cultures and in mammalian (*in vivo*) experimental systems. In particular, the IARC statement that there are indications of oxidative stress in the blood plasma, liver, brain and kidney of rats upon exposure to glyphosate can be supported. However, only one of the cited studies investigated oxidative stress in animals with pure glyphosate. This study was conducted in rats and no other species was tested and increased oxidative stress was observed in combination with cytotoxic/degenerative effects of the targeted organs.

Considering the low level of metabolism and the chemical structure of glyphosate, glyphosate radical formation initiating oxidative stress appears unlikely. However, uncoupling or inhibition of mitochondrial oxidative phosphorylation also represents an established mechanism for ROS generation. Notably, uncoupling of oxidative phosphorylation by glyphosate has been reported in rat liver microsomes and a glyphosate formulation (but not glyphosate).

Induction of oxidative stress can provide a mechanistic explanation for any observed cytotoxic/degenerative and indirectly genotoxic effects of substances. However, from the sole observation of oxidative stress and the existence of a plausible mechanism for induction of oxidative stress through uncoupling of mitochondrial oxidative phosphorylation alone, genotoxic or carcinogenic activity in humans cannot be deduced for glyphosate and glyphosate based formulations.

Furthermore, the RMS concludes that the evidence from available data do not allow to conclude that glyphosate caused immunosuppression.

Glyphosate was included into the U.S. EPA Endocrine Disruptor Screening Program's (EDSP). Which concluded that, based on the Tier 1 assays that had been performed at different independent laboratories and taking into account the 'higher tier' regulatory safety studies Glyphosate might not be considered an endocrine disrupter.

5.5 Further conclusions and recommendations

In result of the now available additional data and information on glyphosate formulations it is concluded and recommended:

- The data requirement for the evaluation and authorisation of plant protection products should be general verified and extended, in particular in consideration of possible genotoxic properties and effects caused by the mixture of different active substances or in combination with co-formulants. The described information on the genotoxicity of the different glyphosate formulations show clearly that a prediction on the genotoxicity based on the single ingredients of a formulation according to the CLP-Regulation (ECHA, 2013, ASB2015-8592) is insufficient. Therefore, in general a specific data requirement for the evaluation and assessment of genotoxic properties of plant protection products is necessary.
- For the representative formulation for the EU renewal procedure 'Roundup Ultra' two studies ([redacted] 2012, ASB2014-7619, [redacted] 2014, ASB2015-8631) reported positive results in comet assays using the European eel as test species. According to Point 7.1.7 of Regulation (EU) No 284/2013 (EU, 2013, ASB2015-8658) the competent Authorities have to discuss case by case the need to perform supplementary studies. The RMS recommends further genotoxicity studies performed in compliance with OECD test guidelines for the representative formulation as confirmatory information for the authorisation of plant protection products.

IARC Monographs are written by a Working Group (WG) over a period of about 12 months to evaluate all of the scientific literature on a given substance and, through a transparent and rigorous process[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS </title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></ /related-urls></urls></record></Cite></EndNote>], reach a decision on the degree to which the scientific literature supports the ability of that substance to cause cancer. For Monograph 112[ADDIN EN.CITE <EndNote><Cite><Author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans</Author><Year>2015</Year><RecNum>3933</RecNum><DisplayText>[2]</DisplayText><record><rec-number>3933</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1438346335">3933</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC Working Group on the Evaluation of Carcinogenic Risks to Humans,</author></authors><secondary-authors><author>IARC Monographs Program</author></secondary-authors></contributors><titles><title>Glyphosate</title><secondary-title>IARC Monogr Eval Carcinog Risks Hum</secondary-title><alt-title>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</alt-title></titles><periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></periodical><alt-periodical><full-title>IARC Monogr Eval Carcinog Risks Hum</full-title><abbr-1>IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer</abbr-1></alt-periodical><pages>1-92</pages><volume>112</volume><keywords><keyword>Animals</keyword><keyword>Biological Markers</keyword><keyword>Carcinogenicity Tests</keyword><keyword>Carcinogens, Environmental/*analysis/toxicity</keyword><keyword>Causality</keyword><keyword>Glyphosate</keyword><keyword>Herbicides</keyword><keyword>Environmental Exposure/adverse effects/*analysis/statistics & numerical data</keyword><keyword>Humans</keyword><keyword>Time

Factors</keyword></keywords><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The WG concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and lead to a careful evaluation of the IARC monograph results when they came available on July 29, 2015. On August 31, 2015, the German Federal Institute for Risk Assessment (BfR) completed an addendum[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2015</Year><RecNum>3962</RecNum><DisplayText>[3]</DisplayText><record><rec-number>3962</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652969">3962</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Assessment of IARC Monographies Volume 112 (2015): Glyphosate</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.bfr.bund.de/cm/343/behoerden-der-eu-mitgliedstaaten-bescheinigen-der-bfr-bewertung-der-iarc-monographie-zu-glyphosat-hohe-wissenschaftliche-qualitaet-und-aussagekraft.pdf</url></related-urls></urls></record></Cite></EndNote>] (the BfR Addendum) to the Draft Renewal Assessment Report[ADDIN EN.CITE <EndNote><Cite><Author>German Federal Institute for Risk Assessment</Author><Year>2013</Year><RecNum>3964</RecNum><DisplayText>[4]</DisplayText><record><rec-number>3964</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653708">3964</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>German Federal Institute for Risk Assessment,</author></authors></contributors><titles><title>Renewal Assessment Report</title></titles><dates><year>2013</year></dates><urls><related-urls><url>http://dar.efsa.europa.eu/dar-web/provision</url></related-urls></urls></record></Cite></EndNote>] (RAR) for glyphosate. This addendum was leaked by the media[ADDIN EN.CITE <EndNote><Cite><Author>Das Erste</Author><Year>2015</Year><RecNum>3963</RecNum><DisplayText>[5]</DisplayText><record><rec-number>3963</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446653250">3963</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Das Erste,</author></authors></contributors><titles><title>BfRBewertung zu Glyphosat</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html</url></related-urls></urls></record></Cite></EndNote>]. This letter is in response to the BfR Addendum and all signatories of this letters were members of the IARC WG for Monograph 112.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "limited evidence in humans for the carcinogenicity of glyphosate". In the IARC review process, this is defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] The BfR Addendum (p. ii) then characterizes the IARC interpretation as "precautionary" and takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and third argument for the end of our letter.

The finding of "limited evidence" by the IARC WG was for non-Hodgkins lymphoma (NHL). When done correctly, cohort studies are very important in determining the carcinogenicity of an agent because they generally have less chance for bias, confounding and missclassification than case-control studies. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The BfR refers to this study as "the most powerful study" and that it was negative for NHL. The study had a very weak positive finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. Had this been the only study available, the WG would certainly not have classified glyphosate as "limited evidence".

The potential limitations with case-control studies can be found in any competent epidemiology textbook [ADDIN EN.CITE <EndNote><Cite><Author>Checkoway</Author><Year>2004</Year><RecNum>3965</RecNum><DisplayText>[6]</DisplayText><record><rec-number>3965</rec-number><foreign-keys><key app="EN" db-

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Methods.</keyword><keyword>Occupational Exposure.</keyword><keyword>Risk
Assessment.</keyword></keywords><dates><year>2004</year></dates><pub-
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Press</publisher><isbn>0195092422 (cloth alk. paper)</isbn><accession-
num>13187775</accession-num><call-num>RC964 .C42 2004</call-
num><urls><related-urls><url>Table of contents only
http://www.loc.gov/catdir/toc/fy043/2003053095.html</url><url>Publisher
description http://www.loc.gov/catdir/enhancements/fy0614/2003053095-
d.html</url></related-urls></urls></record></Cite></EndNote>] and the BfR uses
these to list all of the case-control studies as unreliable. This gives the impression that
all of the studies are equal in quality and unusable for an overall evaluation. This is not
the case. An IARC WG carefully evaluates all of the available epidemiology data, looking
at the study's strengths and weaknesses as well as the study order. This is key in
determining whether the positive associations seen are a reliable indication of an
association or simply a chance finding. Finally, the meta-analysis cited in the IARC
Monograph[ADDIN EN.CITE
<EndNote><Cite><Author>Schinasi</Author><Year>2014</Year><RecNum>3966</R
ecNum><DisplayText>[7]</DisplayText><record><rec-number>3966</rec-
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L.</author><author>Leon, M. E.</author></authors></contributors><auth-
address>Section of Environment and Radiation, International Agency for Research on
Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France.
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Section of Environment and Radiation, International
Agency for Research on Cancer 150, Cours Albert Thomas, 69372 Lyon Cedex 08,
France. leonrouxm@iarc.fr.</auth-address><titles><title>Non-Hodgkin lymphoma and
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Health</full-title><abbr-1>International journal of environmental research and public
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1660-4601 (Linking)</isbn><accession-num>24762670</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/24762670</url></related-urls></urls><custom2>PMC4025008</custom2><electronic-resource-num>10.3390/ijerph110404449</electronic-resource-num></record></Cite></EndNote>] and redone by the WG is the best method for evaluating if there is a consistent positive trend; this meta-analysis showed a statistically significant association. The BfR concludes (p. 22) "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate". We agree, but still consider that an association is observed, that causality is credible and that these findings should be used as part of the overall evaluation.

Evidence from Chronic Exposure Animal Studies

We are astonished by the conclusions of the BfR regarding the animal carcinogenicity data. In the IARC WG review, we found a significant positive trend for renal tumors in CD-1 mice[ADDIN EN.CITE <EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[8]</DisplayText><record><rec-number>3421</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>] and since this was a rare tumor, compared it to an appropriate historical control dataset[ADDIN EN.CITE <EndNote><Cite><Author>Chandra</Author><Year>1994</Year><RecNum>3967</RecNum><DisplayText>[9]</DisplayText><record><rec-number>3967</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446654529">3967</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chandra, M.</author><author>Frith, C. H.</author></authors></contributors><auth-address>Experimental Pathology Department, American Cyanamid Company, Little Rock, Arkansas.</auth-address><titles><title>Spontaneous renal lesions in CD-1 and B6C3F1 mice</title><secondary-title>Exp Toxicol Pathol</secondary-

title></titles><periodical><full-title>Exp Toxicol Pathol</full-title></periodical><pages>189-98</pages><volume>46</volume><number>3</number><keywords><keyword>Adenoma/pathology/veterinary</keyword><keyword>Animals</keyword><keyword>Carcinoma, Renal Cell/pathology/veterinary</keyword><keyword>Female</keyword><keyword>Kidney Diseases/pathology/*veterinary</keyword><keyword>Kidney Neoplasms/pathology/*veterinary</keyword><keyword>Male</keyword><keyword>Mice</keyword><keyword>*Mice, Inbred Strains</keyword><keyword>Rodent Diseases/*pathology</keyword></keywords><dates><year>1994</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0940-2993 (Print)
0940-2993 (Linking)</isbn><accession-num>8000238</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/8000238</url></related-urls></urls><electronic-resource-num>10.1016/S0940-2993(11)80080-1</electronic-resource-num></record></Cite></EndNote>] for CD-1 mice demonstrating even greater significance. A significant positive trend means that as the exposure increases, the pattern seen in the data supports an increasing risk with increasing dose. There were no significant comparisons of any individual exposure group to the control group, however the high exposure group was highly significantly different the historical control population. We also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[ADDIN EN.CITE <EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNum><DisplayText>[10]</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1385988909">611</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>JCFA</author></authors></contributors><titles><title>Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-location><publisher>Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization</publisher><isbn>WHO Technical Series #884</isbn><urls></urls></record></Cite></EndNote>], again with no individual exposure group significantly different from controls. Finally, we also saw a significant increase in the incidence of islet cell adenomas in two studies in Sprague-Dawley rats[ADDIN EN.CITE ADDIN EN.CITE.DATA]. In one of these rat studies, thyroid adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mice studies we examined and for benign tumors in 2 of the five rat studies we examined. By the IARC review criteria[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-

type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>], the evidence in the mouse constitutes sufficient evidence in animals. The BfR agreed, stating (p. 44) "it is obvious that IARC concludes on "sufficient evidence of carcinogenicity" because the criteria for this conclusion are fully met."

It was clear at the time of our review that other studies had been done, but they were not publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>]). Based on the BfR Addendum, it seems there were 3 additional mouse studies and 2 additional rat studies where they had sufficient evidence to review the findings. Remarkably, the findings of these studies independently replicated the studies reported in the Monograph. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[ADDIN EN.CITE <EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sugimoto</author></authors></contributors><titles><title>18-Month Oral Oncogenicity Study in Mice</title><secondary-title>Unpublished, designated ASB2012-11493 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ASB2012-11493 in BfR RAR</full-title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>], and one in Swiss-Webster mice[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2001</Year><RecNum>3969</RecNum><DisplayText>[15]</DisplayText><record><rec-number>3969</rec-number><foreign-keys><key app="EN" db-

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></EndNote>]. One of these studies[ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
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title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite
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reported two studies in CD-1 mice showing significant trends for malignant lymphoma[
ADDIN EN.CITE
<EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</
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type><contributors><authors><author>Unknown</author></authors></contributors
><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the
Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR
RAR</secondary-title></titles><periodical><full-title>Unpublished, designated
ABS2012-11492 in BfR RAR</full-
title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite

></EndNote>]. For all of the tumors described above in CD-1 mice, a positive trend was seen against the concurrent control.

However, in all cases in CD-1 mice, including those observed by the IARC, the BfR dismisses the observed tumors because there are no treatment groups which are significantly different from controls and because the maximum observed response is within the range of the historical control data (Table 5.3-1 in the Addendum). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>] and publications[ADDIN EN.CITE ADDIN EN.CITE.DATA] on the issue, the first choice should be the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, it should be from the same timeframe for the exact strain, preferably from the same laboratory or the same supplier and preferably with the same pathologist[ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2012</Year><RecNum>3971</RecNum><DisplayText>[17]</DisplayText><record><rec-number>3971</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446658807">3971</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>OECD</author></authors><secondary-authors><author>Environment, Health and Safety Publications</author></secondary-authors></contributors><titles><title>Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies</title><tertiary-title>Series on Testing and Assessment</tertiary-title></titles><dates><year>2012</year></dates><pub-location>Paris</pub-location><publisher>OECD</publisher><urls></urls></record></Cite></EndNote>]. This was not the case for the historical control database used by BfR. One of the mouse studies[ADDIN EN.CITE <EndNote><Cite><Author>Epa</Author><Year>1985</Year><RecNum>3421</RecNum><DisplayText>[8]</DisplayText><record><rec-number>3421</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"

timestamp="1424277161">3421</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Epa,</author></authors><secondary-authors><author>William Dykstra.Toxicology, Branch</author></secondary-authors></contributors><titles><title>Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study</title></titles><volume>Accession No. 251007-014. Tox review 004370</volume><keywords><keyword>Vol 112</keyword><keyword>Glyphosate</keyword><keyword>PDF</keyword><keyword>Glyphosate_Sect3_Jameson_quoted</keyword></keywords><dates><year>1985</year></dates><urls><related-urls><url>http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/103601/103601.htm</url><url>file://\\inti\cie\Swap\Vol112\PDFs\Glyphosate\EPA.1985.Glyphosate...mouse.oncogenicity.study.pdf</url></related-urls></urls></record></Cite></EndNote>] was clearly done before this historical control database was developed, one study[ADDIN EN.CITE <EndNote><Cite><Author>Sugimoto</Author><Year>1997</Year><RecNum>3968</RecNum><DisplayText>[14]</DisplayText><record><rec-number>3968</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446656337">3968</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sugimoto</author></authors></contributors><titles><title>18-Month Oral Oncogenicity Study in Mice</title><secondary-title>Unpublished, designated ASB2012-11493 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ASB2012-11493 in BfR RAR</full-title></periodical><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] used Crj:CD-1 mice rather than Crl:CD-1 mice, and 1 study[ADDIN EN.CITE <EndNote><Cite><Author>JCFA</Author><Year>1999</Year><RecNum>611</RecNum><DisplayText>[10]</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1385988909">611</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>JCFA</author></authors></contributors><titles><title>Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives</title></titles><pages>96</pages><dates><year>1999</year><pub-dates><date>1999</date></pub-dates></dates><pub-location>Geneva</pub-location><publisher>Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization</publisher><isbn>WHO Technical Series #884</isbn><urls></urls></record></Cite></EndNote>] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2009</Year><RecNum>3970</RecNum><DisplayText>[16]</DisplayText><record><rec-number>3970</rec-number><foreign-keys><key app="EN" db-

id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446657481">3970</key></foreign-keys><ref-type name="Journal
Article">17</ref-
type><contributors><authors><author>Unknown</author></authors></contributors
><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the
Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR
RAR</secondary-title></titles><periodical><full-title>Unpublished, designated
ABS2012-11492 in BfR RAR</full-
title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite
></EndNote>] used the right strain, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</Rec
Num><DisplayText>[21]</DisplayText><record><rec-number>3975</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446660626">3975</key></foreign-keys><ref-type
name="Report">27</ref-type><contributors><authors><author>Giknis,
M.</author><author>Clifford,
C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions
in the CrI:CD-1(ICR)BR
Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River
Laboratories</publisher><urls><related-
urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_
mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] was from studies in 7 laboratories using the Charles River Laboratory CD1 mice. Surprisingly, there is a second report[ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</Rec
Num><DisplayText>[22]</DisplayText><record><rec-number>3976</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446660642">3976</key></foreign-keys><ref-type
name="Report">27</ref-type><contributors><authors><author>Giknis,
M.</author><author>Clifford,
C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions
in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year
Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River
Laboratories</publisher><urls><related-
urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_m
ouse.aspx</url></related-urls></urls></record></Cite></EndNote>] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[ADDIN EN.CITE
<EndNote><Cite><Author>Giknis</Author><Year>2000</Year><RecNum>3975</Rec
Num><DisplayText>[21]</DisplayText><record><rec-number>3975</rec-
number><foreign-keys><key app="EN" db-
id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a"
timestamp="1446660626">3975</key></foreign-keys><ref-type

name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford, C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse</title></titles><dates><year>2000</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crl_cd_icr_br_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows 5 and 4 studies out of 46 with adenomas and adenocarcinomas respectively whereas the 2005 report[ADDIN EN.CITE <EndNote><Cite><Author>Giknis</Author><Year>2005</Year><RecNum>3976</RecNum><DisplayText>[22]</DisplayText><record><rec-number>3976</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446660642">3976</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Giknis, M.</author><author>Clifford, C.</author></authors></contributors><titles><title>Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies</title></titles><dates><year>2005</year></dates><publisher>Charles River Laboratories</publisher><urls><related-urls><url>http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_mouse.aspx</url></related-urls></urls></record></Cite></EndNote>] shows only 1 study each out of 54 with a single adenoma and a single adenocarcinoma; all other studies had no tumors. Finally, in one mouse study[ADDIN EN.CITE <EndNote><Cite><Author>Unknown</Author><Year>2009</Year><RecNum>3970</RecNum><DisplayText>[16]</DisplayText><record><rec-number>3970</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446657481">3970</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Unknown</author></authors></contributors><titles><title>Glyphosate Technical: Dietary Carcinogencity Study in the Mouse</title><secondary-title>Unpublished, designated ABS2012-11492 in BfR RAR</secondary-title></titles><periodical><full-title>Unpublished, designated ABS2012-11492 in BfR RAR</full-title></periodical><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] with malignant lymphomas, the comparison of the high exposure group to the control using four tests as reported by the BfR (Table 3-7) yielded p-values of 0.022, 0.022, 0.056 and 0.067; it is hard to see how this comparison to control can be disregarded.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that the evidence we were not allowed to see was overwhelmingly negative and that, since the studies we did

review were not done under guideline principles, they should get less weight. No consideration is given to the different strains and cell lines studied in the literature when compared to the guideline studies; no consideration is given to the different endpoints provided in the literature data; and the human in-vivo evidence is completely ignored. Because we are not able to evaluate the data that is proprietary, we are unable to comment on the veracity of their claim, but will note that, like the animal carcinogenicity data, the evaluations (Tables 4.2.1 to 4.2.7) seem to be simple and possibly miss dose-response trends.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but do not agree that this is strong support for an oxidative stress mechanism. They reduce the significance of these findings predominantly because of a lack of positive controls and because many of the studies used glyphosate formulations and not pure glyphosate. The WG disagrees with the BfR. We concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". Hence, based on the studies we reviewed, not only were we able to identify glyphosate as inducing oxidative stress, but the formulations and AMPA as well.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A. In their 2013 Draft RAR, BfR concluded (Vol. 1, p. 139) "classification and labelling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential". How is this possible? Let's review the evidence and the conclusions.

The IARC WG saw an association between NHL and glyphosate in the human evidence, but could not rule out chance, bias and confounding; the IARC definition of "limited evidence"[ADDIN EN.CITE <EndNote><Cite><Author>IARC</Author><Year>2006</Year><RecNum>3961</RecNum><DisplayText>[1]</DisplayText><record><rec-number>3961</rec-number><foreign-keys><key app="EN" db-id="p09svwe0otsedoevra65a0dg5wz9t2zw5f2a" timestamp="1446652347">3961</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>IARC</author></authors><secondary-authors><author>IARC Monographs</author></secondary-authors></contributors><titles><title>PREAMBLE TO THE IARC MONOGRAPHS</title></titles><pages>25</pages><dates><year>2006</year></dates><pub-location>Lyon, France</pub-location><urls><related-urls><url>http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf</url></related-urls></urls></record></Cite></EndNote>] for epidemiological data. BfR agreed, noting that other IARC categories are "not suitable". However the BfR concluded that an association was seen but dismissed it as insufficiently consistent.

The IARC WG saw significant effects for two tumors in two mouse studies and benign tumors in two rat studies. The BfR confirmed the statistically significant findings by the IARC WG, and agreed that the IARC criteria of "sufficient" evidence in animals is "fully met". BfR went on to identify two more mouse studies (bringing it to 3) with kidney tumors and another mouse study (bringing it to 2) with an increase in hemangiosarcoma, and two mouse studies showing increases in malignant lymphoma. Thus, all five mouse studies examined by the BfR were positive in at least 1 tumor site, 1 was positive in 3 tumor sites. Then using an inappropriate historical control dataset in an inappropriate way, dismiss all of these findings as chance.

The IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available data. The BfR, while confirming the positive studies we saw for genotoxicity dismissed them because they were not guideline studies and because, in their interpretation, all of the guideline assays were negative. The BfR confirmed the positive studies we saw for oxidative stress, noted some concern over these data, but concluded they could not use them because there were no other data to support a finding of carcinogenicity or genotoxicity and the mechanism cannot stand alone.

The basis of the IARC evaluation was the "limited evidence" in humans and the "sufficient evidence" in animals, conclusions the BfR note are consistent with the IARC criteria, with supporting evidence of 2 strong mechanisms. Is glyphosate the agent causing this hazard? Given the human evidence (co-formulants only), the animal evidence (glyphosate only) and the mechanistic evidence (all forms), the most logical scientific conclusion is that glyphosate is the probable carcinogen. The BfR dismissed all evidence in humans, dismissed all evidence in animals and concluded there was one weak mechanism that could not be used in isolation.

We feel that the process used by the BfR to review human and animal evidence is fundamentally flawed and should be reconsidered. We are of the opinion that the scientific basis for rejecting the human, animal and mechanistic studies is non-existent and appears to have been designed to achieve a pre-determined goal rather than an objective scientific review. Finally, we strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide.

We stand by our conclusion that glyphosate is a probable human carcinogen.

[ADDIN EN.REFLIST]

Appointment

From: Gentry, Nathan [Gentry.Nathan@epa.gov]
Sent: 11/4/2015 7:27:18 PM
To: Martin, Matt [Martin.Matt@epa.gov]; Egeghy, Peter [Egeghy.Peter@epa.gov]

Subject: FW: Glyphosate Human Health meeting
Attachments: glyphosate tom burke briefing slide deck 11 4 15 aftn revised.pptx
Location: DCRoomRRB41213/ORD; call in Ex. 6 - Personal Privacy

Start: 11/5/2015 8:00:00 PM
End: 11/5/2015 9:00:00 PM
Show Time As: Tentative

-----Original Appointment-----
From: Jones, Jim
Sent: Monday, November 02, 2015 4:12 PM
To: Jones, Jim; Wise, Louise; Mojica, Andrea; Burke, Thomas; Gentry, Nathan; Smith, Kelley; Deener, Kathleen; Jordan, William; Monell, Marty; Vogel, Dana; Rowland, Jess; Lowit, Anna; Smith, Charles; Morton, Thurston; Perron, Monique; Dunbar, Anwar; Akerman, Gregory; Bloem, Thomas; Middleton, Karlyn; Dawson, Jeffrey; Lobdell, Danelle; Wood, Charles; Nguyen, Thuy; Dix, David
Cc: Dinkins, Darlene; Venkateshwara, Lata; Kavlock, Robert; Bahadori, Tina; Fegley, Robert; McQueen, Jacqueline; Birchfield, Norman; Cogliano, Vincent
Subject: Glyphosate Human Health meeting
When: Thursday, November 05, 2015 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomRRB41213/ORD; call in Ex. 6 - Personal Privacy

glyphosate tom burke briefing sli...

Message

From: Thomas, Kent [thomas.kent@epa.gov]
Sent: 3/20/2015 7:47:38 PM
To: Egeghy, Peter [Egeghy.Peter@epa.gov]
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)
Attachments: Lancet Onco. Carcinogenicity of tetrachlorvinphos, parathion, malathion....pdf

Just in case you hadn't already seen it. It sure came out fast.
Kent

-----Original Message-----
From: Miller, David
Sent: Friday, March 20, 2015 2:20 PM
To: Thomas, Kent
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI - I am sure you will get this soon, if you haven't already.

Carol provides the link below, if you prefer that.

David.

David J. Miller CAPT | USPHS
Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch Health Effects Division Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)
Visit www.epa.gov/pesticides

-----Original Message-----
From: Miller, David
Sent: Friday, March 20, 2015 2:16 PM
To: OPP HED Managers
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI - it's now out...

David.

-----Original Message-----
From: Miller, David
Sent: Friday, March 20, 2015 1:57 PM
To: Christensen, Carol; Britton, Wade; Rowland, Jess
Cc: Vogel, Dana
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Thanks, Carol.

I've attached the downloaded PDF of the article to make it simpler for folks.

David.

-----Original Message-----
From: Christensen, Carol
Sent: Friday, March 20, 2015 1:24 PM
To: Britton, Wade; Miller, David; Rowland, Jess
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI: http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf

---

From: Christensen, Carol
Sent: Friday, March 20, 2015 11:53 AM
To: Britton, Wade; Miller, David; Rowland, Jess

Subject: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Hi All

I just learned that the summary of the IARC-pesticide meeting is expected to be available on line around 1 pm today. FYI.

I think this is the link: http://www.thelancet.com/journals/lanonc/issue/current.

Carol

Message

From: Kurt Straif [StraifK@iarc.fr]
Sent: 3/20/2015 5:25:18 PM
To: lin.fritschi@curtin.edu.au; h.kromhout@uu.nl; Egeghy, Peter [Egeghy.Peter@epa.gov]; Ex. 6 - Personal Privacy isabelle.baldi@isped.u-bordeaux2.fr; Ex. 6 - Personal Privacy f.forastiere@deplazio.it; john.mclaughlin@oahpp.ca; a.mannetje@massey.ac.nz; rafaelc@mor.org.il; Sonia El-Zaemey [ElzaemeyS@fellows.iarc.fr]; Charlotte Le Cornet [LeCornetC@students.iarc.fr]; Maria Leon Roux [leonrouxm@iarc.fr]; GMC24@columbia.edu; jahnke@niehs.nih.gov; drjameson@embarqmail.com; sergi@ualberta.ca; frank.lecurieux@echa.europa.eu; Martin, Matt [Martin.Matt@epa.gov]; Ex. 6 - Personal Privacy mross@cvm.msstate.edu; irusyn@cvm.tamu.edu; Ex. 6 - Personal Privacy Jiri Zavadil [ZavadilJ@iarc.fr]
CC: imo-all@iarc.fr; Nicolas Gaudin [GaudinN@iarc.fr]
Subject: IARC Monographs, Vol 112, TLO and mews piece
Attachments: News Item Monograph Volume 112.pdf; TLO_V112_PIIS1470204515701348.pdf

Dear all,

Thank you again for your most important contributions to develop this IARC Monograph.
The TLO summary report (also accessible after free registration) and an IARC news piece are attached here.

Best regards,
Kurt

Kurt Straif, MD PhD MPH
Head IARC Monographs
International Agency for Research on Cancer
World Health Organization
150 cours Albert Thomas
69372 Lyon Cedex 08, France
Tel +33 (0)472 73 85 07 (PA)
Fax +33 (0)472 73 83 19
http://monographs.iarc.fr

Message

From: Kromhout, J. (Hans) [h.kromhout@uu.nl]
Sent: 3/16/2015 6:48:50 AM
To: Kathryn Guyton [GuytonK@iarc.fr]; Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez [Ex. 6 - Personal Privacy] Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi [Ex. 6 - Personal Privacy] Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise [[Ex. 6 - Personal Privacy] Christopher Portier [Ex. 6 - Personal Privacy]
CC: imo-pro@iarc.fr
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft
Attachments: TLO_vol 112_13 March 2015+HK.docx

Importance: High

Hi Kathryn,

The write up looks pretty good. In the attachment my comments in track changes in the word document. I missed a few lines (short paragraph) on the issues we wrote up on exposure assessment and the multiple exposure situations all epi-studies have to deal with. I think it would be good to have that in the Lancet Oncology as well.

Best and good luck with the submission, Hans

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: Friday, March 13, 2015 3:35 PM
To: Isabelle Baldi; Blair, Aaron (NIH/NCI) [V]; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: imo-pro@iarc.fr
Subject: IARC Monograph vol 112- Lancet oncology article draft

Dear all,

We thank you again for your outstanding contributions to the IARC Monograph volume 112 meeting!

We provide for your review and comment no later than Monday COB in your time zone a draft of the Lancet Oncology article. We ask for your feedback using track changes, preferably using the google doc sent separately or in the appended Word file. Please turn on track changes before entering any suggested edits. We strongly prefer direct edits to the text but will attempt to address any comments as well.

Please be reminded that the information summarised herein is strictly embargoed until the Lancet Oncology article is published online. We will be pleased to inform you when this has occurred.

My very best regards,
With thanks to you all,
Kate
Kate Z. Guyton PhD DABT
Responsible Officer, Volume 112
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<mailto:Guytonk@iarc.fr>

Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon and Glyphosate

In March 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of organophosphate pesticides, including tetrachlorvinphos, parathion, malathion, diazinon and glyphosate (see Table). These assessments will be published as Volume 112 of the IARC Monographs (IARC).

The insecticides tetrachlorvinphos and parathion were classified as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals. Tetrachlorvinphos is banned in the European Union (EU). In the US, it continues to be used on animals, including in pet flea collars. Although excesses for non-Hodgkin lymphoma (NHL), leukemia and brain cancer were observed in the few studies that assessed tetrachlorvinphos use, the overall evidence from human studies remains inadequate. Tetrachlorvinphos induced mouse (benign or malignant) hepatocellular tumours, male mouse (benign or malignant) renal tubule tumours (Parker et al., 1985), male rat spleen haemangioma and female rat thyroid C-Cell and adrenal cortical adenomas. Tetrachlorvinphos is a reactive oxon with affinity for esterases. ~~One human study suggested dermal absorption.~~ In experimental animals, tetrachlorvinphos is systemically distributed, metabolized, and eliminated in urine. Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and *in vitro*) and increased proliferation (hyperplasia in rodents).

Parathion has been severely restricted beginning in the 1980s, with all authorizations banned in the EU and US by 2003. The evidence for cancer in humans remains sparse, with no replication of the few cancer associations detected (including for NHL, melanoma, prostate and breast). In mice, parathion increased bronchioloalveolar tumours in males and lymphoma in females (EPA, 1991). In rats, parathion induced adrenal cortical tumours (NTP, 1979). Other rat neoplasms included (benign or malignant) pancreatic tumours and thyroid follicular cell adenomas in males, and mammary gland fibroadenomas (adenocarcinomas following subcutaneous injection during ductal morphogenesis (Cabello et al., 2011)) in females. Parathion is rapidly absorbed and distributed from the gastrointestinal tract in humans, but dermal absorption is ~~less~~ not efficient. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density (Cabello et al., 2001).

The insecticides malathion and diazinon were classified as Group 2A (probably carcinogenic to humans). Malathion has a wide range of uses in agriculture, and residential insect control~~, and public health~~. Malathion continues to be produced in substantial volumes throughout the world and is currently being re-registered for use in Europe. Population exposure is generally low and occurs primarily through diet, residence near sprayed areas, and home uses. There is limited evidence in humans for ~~the~~ malathion carcinogenicity. Case-control analyses reported positive associations with NHL in the US (Waddell et al., 2001; Mills et al., 2005), Canada (McDuffie et al., 2001) and Sweden (Eriksson et al., 2008), although no NHL excesses were observed in the large Agricultural Health Study cohort (AHS). Malathion use was associated with an increased risk of prostate cancer in a Canadian case–control study and in the AHS. The AHS reported a significant trend only for

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aggressive cancers after adjustment for other pesticides (Koutros 2012) and an effect of genetic polymorphisms related to prostate cancer susceptibility (Koutros et al., 2013). In rodents, malathion induced mouse (benign or malignant) hepatocellular tumours (EPA, 1994), rat thyroid carcinomas and rat hepatocellular tumours (females). Separate rat studies reported pheochromocytoma (males); occurrence of rare tumours of the nasal pharyngeal and oral cavity; and female mammary gland fibroadenoma (adenocarcinoma following subcutaneous injection during ductal morphogenesis (Cabello et al., 2001)) and uterine polyps. Malathion is rapidly absorbed and distributed following oral exposure, but dermal absorption is ~~less~~ not efficient. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malathion induces DNA and chromosomal damage in human studies, corroborated by animal and in vitro studies. Bacterial tests were negative. Compelling evidence supports disruption of thyroid and androgen hormone pathways. Hormonal effects (rather than cytotoxicity) may mediate rodent thyroid and mammary gland proliferation. Malaoxon strongly inhibits esterases; atropine ameliorated carcinogenesis-related effects in one study (Cabello et al., 2001). Oxidative stress has been challenged experimentally.

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Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and have reduced further since its restriction in the US and the EU. There is limited evidence in humans for the carcinogenicity of diazinon. Positive associations for NHL, with indications of an exposure-response, were reported by two large multicenter case–control studies (Waddell et al., 2001; McDuffie et al., 2001) and the AHS (Alavanja et al., 2014). Confounding by exposure to other pesticides could not explain these findings. An increased leukemia risk reported in several studies was strengthened by a monotonic increase in risk with cumulative diazinon exposure robust to adjustment for exposure to other pesticides. Multiple updates from the AHS consistently demonstrated an increased lung cancer risk with an exposure-response association, arguing against a chance finding, with no evidence of confounding by exposure to other pesticides, smoking, or other established lung cancer risk factors (Jones et al., 2015). Nonetheless, this finding was not replicated in other populations. Thus, despite positive associations and exposure-response trends for NHL, leukemia and lung cancer, there were few studies and confounding by exposure other pesticides could not be excluded. In rodents, diazinon increased mouse hepatocellular carcinoma and rat leukaemia or lymphoma (combined) incidences, but only in low dose males of each study. Diazinon induced DNA or chromosomal damage in rodents and in human and mammalian cells in vitro. Additional support for human relevance is provided by a positive study of a small number of volunteers exposed to a diazinon formulation (Hatjian et al., 2000). Oxidative stress has been challenged experimentally.

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Glyphosate is currently the highest annual global production volume among herbicides (over 700 000 tonnes in 2012), with uses in over 750 different products. A broad-spectrum herbicide, glyphosate is effective against all plant types. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties. Glyphosate has been detected in air during spraying, in water and in food. Population exposure occurs mainly through diet. There is limited evidence in humans for the carcinogenicity of glyphosate, based on a positive association for NHL. Case-control studies in the United States (De Roos et al., 2003), Canada (McDuffie et al., 2001) and Sweden (Hardell et al., 2002; Eriksson et al., 2008) reported increased risks for NHL that persisted after adjustment for exposure to other pesticides. However, the AHS cohort did not show a significant NHL excess (De

Roos et al., 2005). Observed increases in multiple myeloma were given less weight because chance and confounding by ??? could not be excluded. In male mice, glyphosate induced a positive trend in renal tubule carcinoma, a rare tumour (EPA, 1986). A second study found increased haemangiosarcoma incidence in male mice (WHO/FAO, 2004). Two rat studies showed increased pancreatic islet cell adenoma incidence in males. A commercial formulation was a skin-tumour promoter in a mouse initiation-promotion study.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. In the rat, glyphosate is distributed and the plasma half-life was >1 day. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection following poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induce DNA and chromosomal damage in mammals and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in community residents after spraying of glyphosate with an adjuvant or of a glyphosate formulation (Bolognesi et al., 2009). Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induce oxidative stress in rodents and in vitro. This mechanism has been challenged experimentally. Glyphosate was classified as Group 2A (probably carcinogenic to humans).

Table: Agents assessed by the Monograph 112 Working Group

Agent	**Activity (Current status)**	**Evidence in humans (Cancer Sites)**	**Evidence in animals**	**Supporting mechanistic evidence***	**Group#**
Tetrachlorvinphos	Insecticide (Banned)	Inadequate	Sufficient		2B
Parathion	Insecticide (Banned)	Inadequate	Sufficient		2B
Malathion	Insecticide (Currently used, high production volume)	Limited (NHL, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A
Diazinon	Insecticide (Banned)	Limited (NHL, leukemia,	Limited	Genotoxicity and oxidative stress	2A

		lung)			
Glyphosate	Herbicide (Currently highest worldwide production volume herbicide)	Limited (NHL)	Sufficient	Genotoxicity and oxidative stress	2A

*Strong evidence and operative in humans; #See IARC preamble for explanation of classification system

References

Alavanja MC, Hofmann JN, Lynch CF et al. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS ONE 2014. 9(10):e109332.

Band PR, Abanto Z, Bert J et al. Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate 2011. 71(2):168–83.

Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJ. Biomonitoring of genotoxic risk in agricultural workers from five colombian regions: association to occupational exposure to glyphosate. J Toxicol Environ Health A 2009. 72(15-16):986–97.

Cabello G, Valenzuela M, Vilaxa A et al. A rat mammary tumor model induced by the organophosphorous pesticides parathion and malathion, possibly through acetylcholinesterase inhibition. Environ Health Perspect 2001. 109(5):471–9.

De Roos AJ, Zahm SH, Cantor KP et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 2003. 60(9):E11.

De Roos AJ, Blair A, Rusiecki JA et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect 2003. 113(1):49–54.

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US EPA (1986). Glyphosate EPA Reg 524-308 Roundup:Additional histopathological evaluations of Kidneys in the Chronic Feeding Study of Glyphosate Document 005590.

US EPA (1991). Peer Review of Parathion Oncogenicity Study in the Mouse. MRID 418173-01. Robert Zendzian. Toxicology Branch. Anonymous. 1991. Toxicol Rev. 008429:•••. [HYPERLINK "http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/057501/057501.htm"]

US EPA (1994) Peer Review of Malathion: 18-month carcinogenicity study in mice, International Research and Development Corporation., No. MRID 43407201. Available at: http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-057701_undated_004.pdf

Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008. 123(7):1657–63.

Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002. 43(5):1043–9.

Hatjian BA, Mutch E, Williams FM, Blain PG, Edwards JW. Cytogenetic response without changes in peripheral cholinesterase enzymes following exposure to a sheep dip containing diazinon in vivo and in vitro. Mutat Res 2000. 472(1-2):85–92.

International Agency for Research on Cancer. Volume 112: Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC Working Group. Lyon; 3-10 March 2015. IARC Monogr Eval Carcinog Risk Chem Hum (in press).

Koutros S, Berndt SI, Barry K. Hughes, G. Andreotti, J. A. Hoppin, D. P. Sandler, M. Yeager, L. A. Burdett, J. Yuenger, M. C. Alavanja, and L. E. Beane Freeman. Genetic susceptibility loci, pesticide exposure and prostate cancer risk. PLoS ONE 2013. 8(4):e58195.

McDuffie HH, Pahwa P, McLaughlin JR et al.. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001. 10(11):1155–63.

Mills PK, Yang R, Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes Control 2005. 16(7):823–30.

NTP. Bioassay of parathion for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser 1979. 70:1–123.

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Parker CM, Van Gelder GA, Chai EY, Gellatly JBM, Serota DG, Voelker RW, et al. (1985). Oncogenic evaluation of tetrachlorvinphos in the B6C3F1 mouse. Fundam Appl Toxicol. 5(5):840–54.

Waddell BL, Zahm SH, Baris D et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control 2001. 12(6):509–17.

WHO/FAO (2004). Glyphosate. Pesticides residues in food 2004 Joint FAO/WHO Meeting on Pesticides Residues. Part II Toxicological. IPCS/WHO. 95–162. Available from :[HYPERLINK "http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/"], accessed 6 March 2015.

Margin Info:

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KZ Guyton, D Loomis, Y Grosse, N Guha, L Benbrahim-Tallaa, F El Ghissassi, C Scoccianti, H Mattock and Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France

IARC Monograph Working Group

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L Fritschi (Australia)
CM Sergi; J McLaughlin (Canada)
GM Calaf (Chile)
F Le Curieux (Finland)
I Baldi (France)
F Forastiere (Italy)
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Invited Specialists

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ME Gouze; for the French Agency for Food, Environment and Occupational Health and Safety, France
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B Fervers, for the Léon Bérard Centre, France
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Upcoming meetings

2-9 June 2015, Vol. 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides

6-13 October 2015, Vol. 114: Red Meat and Processed Meat

For more on the IARC Monographs see http://monographs.iarc.fr/

Message

From: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]
Sent: 3/16/2015 7:40:58 AM
To: Kromhout, J. (Hans) [h.kromhout@uu.nl]; Kathryn Guyton [GuytonK@iarc.fr]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy Christopher Portier Ex. 6 - Personal Privacy
CC: imo-pro@iarc.fr
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft
Attachments: TLO_vol 112_13 March2015+HK+IB.docx

Hi Kate and all,

Thank you very much for the draft. I added changes in the attached version revised by Hans: references by Koutros on malathion (Prostate cancer) have to be corrected as mentionned in the comments.
I also have a question to Hans and Linn: would it be useful to mention that glyphosate is not only used in agriculture but also in urban areas (roads, public gardens,...) and in private gardens...?
All the best to you all,

Isabelle

Isabelle BALDI
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-----Original Message-----
From: "Kromhout, J. (Hans)" <h.kromhout@uu.nl>
To: Kathryn Guyton <GuytonK@iarc.fr>, Isabelle Baldi <Isabelle.Baldi@isped.u-bordeaux2.fr>, "Blair, Aaron (NIH/NCI) [V]" <blaira@exchange.nih.gov>, "GMC24@columbia.edu" <GMC24@columbia.edu>, "Egeghy, Peter" <Egeghy.Peter@epa.gov>, "Forastiere, Francesco" <f.forastiere@deplazio.it>, Lin Fritschi <lin.fritschi@curtin.edu.au>, "Jahnke, Gloria (NIH/NIEHS) [E]" <jahnke@niehs.nih.gov>, Bill Jameson <drjameson@embarqmail.com>, frank lecurieux <frank.lecurieux@echa.europa.eu>, Matt Martin <martin.matt@epa.gov>, John McLaughlin <John.McLaughlin@oahpp.ca>, Teresa Rodriguez Ex. 6 - Personal Privacy "Matthew Ross" <MRoss@cvm.msstate.edu>, "Rusyn, Ivan" <IRusyn@cvm.tamu.edu>, Consolato Sergi Ex. 6 - Personal Privacy "Mannetje, Andrea" <A.Mannetje@massey.ac.nz>, Lauren Zeise Ex. 6 - Personal Privacy "Christopher Portier" Ex. 6 - Personal Privacy
Cc: "imo-pro@iarc.fr" <imo-pro@iarc.fr>
Date: Mon, 16 Mar 2015 06:48:50 +0000
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft

Hi Kathryn,

The write up looks pretty good. In the attachment my comments in track changes in the word document. I missed a few lines (short paragraph) on

the issues we wrote up on exposure assessment and the multiple exposure situations all epi-studies have to deal with. I think it would be good to have that in the Lancet Oncology as well.

Best and good luck with the submission, Hans

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: Friday, March 13, 2015 3:35 PM
To: Isabelle Baldi; Blair, Aaron (NIH/NCI) [V]; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: imo-pro@iarc.fr
Subject: IARC Monograph vol 112- Lancet oncology article draft

Dear all,

We thank you again for your outstanding contributions to the IARC Monograph volume 112 meeting!

We provide for your review and comment no later than Monday COB in your time zone a draft of the Lancet Oncology article. We ask for your feedback using track changes, preferably using the google doc sent separately or in the appended Word file. Please turn on track changes before entering any suggested edits. We strongly prefer direct edits to the text but will attempt to address any comments as well.

Please be reminded that the information summarised herein is strictly embargoed until the Lancet Oncology article is published online. We will be pleased to inform you when this has occurred.

My very best regards,
With thanks to you all,
Kate
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Parathion	Insecticide (Banned)	Inadequate	Sufficient		2B
Malathion	Insecticide (Currently used, high production volume)	Limited (NHL, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A
Diazinon	Insecticide (Banned)	Limited (NHL, leukemia,	Limited	Genotoxicity and oxidative stress	2A

		lung)			
Glyphosate	Herbicide (Currently highest worldwide production volume herbicide)	Limited (NHL)	Sufficient	Genotoxicity and oxidative stress	2A

*Strong evidence and operative in humans; #See IARC preamble for explanation of classification system

References

Alavanja MC, Hofmann JN, Lynch CF et al. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS ONE 2014. 9(10):e109332.

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US EPA (1991). Peer Review of Parathion Oncogenicity Study in the Mouse. MRID 418173-01. Robert Zendzian. Toxicology Branch. Anonymous. 1991. Toxicol Rev. 008429:•••. [HYPERLINK "http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/057501/057501.htm"]

US EPA (1994) Peer Review of Malathion: 18-month carcinogenicity study in mice, International Research and Development Corporation., No. MRID 43407201. Available at: http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-057701_undated_004.pdf

Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008. 123(7):1657–63.

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International Agency for Research on Cancer. Volume 112: Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC Working Group. Lyon; 3-10 March 2015. IARC Monogr Eval Carcinog Risk Chem Hum (in press).

Koutros S, Berndt SI, Barry K. Hughes, G. Andreotti, J. A. Hoppin, D. P. Sandler, M. Yeager, L. A. Burdett, J. Yuenger, M. C. Alavanja, and L. E. Beane Freeman. Genetic susceptibility loci, pesticide exposure and prostate cancer risk. PLoS ONE 2013. 8(4):e58195.

McDuffie HH, Pahwa P, McLaughlin JR et al.. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001. 10(11):1155–63.

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Mills PK, Yang R, Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes Control 2005. 16(7):823–30.

NTP. Bioassay of parathion for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser 1979. 70:1–123.

Parker CM, Van Gelder GA, Chai EY, Gellatly JBM, Serota DG, Voelker RW, et al. (1985). Oncogenic evaluation of tetrachlorvinphos in the B6C3F1 mouse. Fundam Appl Toxicol. 5(5):840–54.

Waddell BL, Zahm SH, Baris D et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control 2001. 12(6):509–17.

WHO/FAO (2004). Glyphosate. Pesticides residues in food 2004 Joint FAO/WHO Meeting on Pesticides Residues. Part II Toxicological. IPCS/WHO. 95–162. Available from :[HYPERLINK "http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/"], accessed 6 March 2015.

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Margin Info:

Authors

KZ Guyton, D Loomis, Y Grosse, N Guha, L Benbrahim-Tallaa, F El Ghissassi, C Scoccianti, H Mattock and Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France

IARC Monograph Working Group

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L Fritschi (Australia)
CM Sergi; J McLaughlin (Canada)
GM Calaf (Chile)
F Le Curieux (Finland)
I Baldi (France)
F Forastiere (Italy)
H Kromhout (Netherlands)
A 't Mannetje (New Zealand)
T Rodriguez [unable to attend] (Nicaragua)
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ME Gouze; for the French Agency for Food, Environment and Occupational Health and Safety, France
J Rowland, U.S. Environmental Protection Agency, USA

Observers

MK Boye Jensen, for Cheminova A/S, Denmark
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Upcoming meetings

2-9 June 2015, Vol. 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides

6-13 October 2015, Vol. 114: Red Meat and Processed Meat

For more on the IARC Monographs see http://monographs.iarc.fr/

Message

From: Kromhout, J. (Hans) [h.kromhout@uu.nl]
Sent: 3/16/2015 9:02:44 AM
To: Lin Fritschi [lin.fritschi@curtin.edu.au]; Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Kathryn Guyton [GuytonK@iarc.fr]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy Christopher Portier Ex. 6 - Personal Privacy
CC: imo-pro@iarc.fr
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft

I fully agree, best Hans

From: Lin Fritschi [lin.fritschi@curtin.edu.au]
Sent: Monday, March 16, 2015 9:22 AM
To: Isabelle Baldi; Kromhout, J. (Hans); Kathryn Guyton; Blair, Aaron (NIH/NCI) [V]; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: imo-pro@iarc.fr
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft

Yes I think that sounds like a good addition re the general uses of glyphosate. It's not just agricultural workers who are exposed.

From: Isabelle Baldi [mailto:Isabelle.Baldi@isped.u-bordeaux2.fr]
Sent: Monday, 16 March 2015 3:41 PM
To: Kromhout, J. (Hans); Kathryn Guyton; Blair, Aaron (NIH/NCI) [V]; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: imo-pro@iarc.fr
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft

Hi Kate and all,

Thank you very much for the draft. I added changes in the attached version revised by Hans: references by Koutros on malathion (Prostate cancer) have to be corrected as mentionned in the comments.
I also have a question to Hans and Linn: would it be useful to mention that glyphosate is not only used in agriculture but also in urban areas (roads, public gardens,...) and in private gardens...?
All the best to you all,

Isabelle

Isabelle BALDI
Maître de conférences-Praticien Hospitalier
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ISPED- Université Bordeaux Segalen
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-----Original Message-----
From: "Kromhout, J. (Hans)" <h.kromhout@uu.nl<mailto:h.kromhout@uu.nl>>
To: Kathryn Guyton <GuytonK@iarc.fr<mailto:GuytonK@iarc.fr>>, Isabelle Baldi <Isabelle.Baldi@isped.u-bordeaux2.fr<mailto:Isabelle.Baldi@isped.u-bordeaux2.fr>>, "Blair, Aaron (NIH/NCI) [V]" <blaira@exchange.nih.gov<mailto:blaira@exchange.nih.gov>>, "GMC24@columbia.edu<mailto:GMC24@columbia.edu>" <GMC24@columbia.edu<mailto:GMC24@columbia.edu>>, "Egeghy, Peter" <Egeghy.Peter@epa.gov<mailto:Egeghy.Peter@epa.gov>>, "Forastiere, Francesco" <f.forastiere@deplazio.it<mailto:f.forastiere@deplazio.it>>, Lin Fritschi <lin.fritschi@curtin.edu.au<mailto:lin.fritschi@curtin.edu.au>>, "Jahnke, Gloria (NIH/NIEHS) [E]" <jahnke@niehs.nih.gov<mailto:jahnke@niehs.nih.gov>>, Bill Jameson <drjameson@embarqmail.com<mailto:drjameson@embarqmail.com>>, frank lecurieux <frank.lecurieux@echa.europa.eu<mailto:frank.lecurieux@echa.europa.eu>>, Matt Martin

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Cc: "imo-pro@iarc.fr<mailto:imo-pro@iarc.fr>" <imo-pro@iarc.fr<mailto:imo-pro@iarc.fr>>
Date: Mon, 16 Mar 2015 06:48:50 +0000
Subject: RE: IARC Monograph vol 112- Lancet oncology article draft
Hi Kathryn,

The write up looks pretty good. In the attachment my comments in track changes in the word document. I missed a few lines (short paragraph) on the issues we wrote up on exposure assessment and the multiple exposure situations all epi-studies have to deal with. I think it would be good to have that in the Lancet Oncology as well.

Best and good luck with the submission, Hans

From: Kathryn Guyton [GuytonK@iarc.fr<mailto:GuytonK%40iarc.fr>]
Sent: Friday, March 13, 2015 3:35 PM
To: Isabelle Baldi; Blair, Aaron (NIH/NCI) [V]; GMC24@columbia.edu<mailto:GMC24%40columbia.edu>; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: imo-pro@iarc.fr<mailto:imo-pro%40iarc.fr>
Subject: IARC Monograph vol 112- Lancet oncology article draft

Dear all,

We thank you again for your outstanding contributions to the IARC Monograph volume 112 meeting!

We provide for your review and comment no later than Monday COB in your time zone a draft of the Lancet Oncology article. We ask for your feedback using track changes, preferably using the google doc sent separately or in the appended Word file. Please turn on track changes before entering any suggested edits. We strongly prefer direct edits to the text but will attempt to address any comments as well.

Please be reminded that the information summarised herein is strictly embargoed until the Lancet Oncology article is published online. We will be pleased to inform you when this has occurred.

My very best regards,
With thanks to you all,
Kate
Kate Z. Guyton PhD DABT
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Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 3/13/2015 2:35:52 PM
To: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; GMC24@columbia.edu; Egeghy, Peter [Egeghy.Peter@epa.gov]; Forastiere, Francesco [f.forastiere@deplazio.it]; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; frank lecurieux [frank.lecurieux@echa.europa.eu]; Martin, Matt [Martin.Matt@epa.gov]; John McLaughlin [John.McLaughlin@oahpp.ca]; Teresa Rodriguez Ex. 6 - Personal Privacy Matthew Ross [MRoss@cvm.msstate.edu]; Rusyn, Ivan [IRusyn@cvm.tamu.edu]; Consolato Sergi Ex. 6 - Personal Privacy Mannetje, Andrea [A.Mannetje@massey.ac.nz]; Lauren Zeise Ex. 6 - Personal Privacy Christopher Portier Ex. 6 - Personal Privacy
CC: imo-pro@iarc.fr
Subject: IARC Monograph vol 112- Lancet oncology article draft
Attachments: TLO_vol 112_13 March 2015.docx

Importance: High

Dear all,

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We provide for your review and comment **no later than Monday COB in your time zone** a draft of the Lancet Oncology article. We ask for your feedback using track changes, *preferably using the google doc sent separately* or in the appended Word file. Please turn on track changes before entering any suggested edits. We strongly prefer direct edits to the text but will attempt to address any comments as well.

Please be reminded that the information summarised herein is **strictly embargoed** until the Lancet Oncology article is published online. We will be pleased to inform you when this has occurred.

My very best regards,
With thanks to you all,
Kate

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Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon and Glyphosate

In March 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of organophosphate pesticides, including tetrachlorvinphos, parathion, malathion, diazinon and glyphosate (see Table). These assessments will be published as Volume 112 of the IARC Monographs (IARC).

The insecticides tetrachlorvinphos and parathion were classified as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals. Tetrachlorvinphos is banned in the European Union (EU). In the US, it continues to be used on animals, including in pet flea collars. Although excesses for non-Hodgkin lymphoma (NHL), leukemia and brain cancer were observed in the few studies that assessed tetrachlorvinphos use, the overall evidence from human studies remains inadequate. Tetrachlorvinphos induced mouse (benign or malignant) hepatocellular tumours, male mouse (benign or malignant) renal tubule tumours (Parker et al., 1985), male rat spleen haemangioma and female rat thyroid C-Cell and adrenal cortical adenomas. Tetrachlorvinphos is a reactive oxon with affinity for esterases. One human study suggested dermal absorption. In experimental animals, tetrachlorvinphos is systemically distributed, metabolized, and eliminated in urine. Although bacterial mutagenesis tests were negative, tetrachlorvinphos induced genotoxicity in some assays (chromosomal damage in rats and *in vitro*) and increased proliferation (hyperplasia in rodents).

Parathion has been severely restricted beginning in the 1980s, with all authorizations banned in the EU and US by 2003. The evidence for cancer in humans remains sparse, with no replication of the few cancer associations detected (including for NHL, melanoma, prostate and breast). In mice, parathion increased bronchioloalveolar tumours in males and lymphoma in females (EPA, 1991). In rats, parathion induced adrenal cortical tumours (NTP, 1979). Other rat neoplasms included (benign or malignant) pancreatic tumours and thyroid follicular cell adenomas in males, and mammary gland fibroadenomas (adenocarcinomas following subcutaneous injection during ductal morphogenesis (Cabello et al., 2011)) in females. Parathion is rapidly absorbed and distributed from the gastrointestinal tract in humans, but dermal absorption is less efficient. Parathion metabolism to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density (Cabello et al., 2001).

The insecticides malathion and diazinon were classified as Group 2A (probably carcinogenic to humans). Malathion has a wide range of uses in agriculture, residential insect control, and public health. Malathion continues to be produced in substantial volumes throughout the world. Population exposure is generally low and occurs primarily through diet, residence near sprayed areas, and home uses. There is limited evidence in humans for the malathion carcinogenicity. Case-control analyses reported positive associations with NHL in the US (Waddell et al., 2001; Mills et al., 2005), Canada (McDuffie et al., 2001) and Sweden (Eriksson et al., 2008), although no NHL excesses were observed in the large Agricultural Health Study cohort (AHS). Malathion use was associated with an increased risk of prostate cancer in a Canadian case–control study and in the AHS. The AHS reported a significant trend only for aggressive cancers after adjustment for other pesticides (Koutros 2012) and an effect

of genetic polymorphisms related to prostate cancer susceptibility (Koutros et al., 2013). In rodents, malathion induced mouse (benign or malignant) hepatocellular tumours (EPA, 1994), rat thyroid carcinomas and rat hepatocellular tumours (females). Separate rat studies reported pheochromocytoma (males); occurrence of rare tumours of the nasal pharyngeal and oral cavity; and female mammary gland fibroadenoma (adenocarcinoma following subcutaneous injection during ductal morphogenesis (Cabello et al., 2001)) and uterine polyps. Malathion is rapidly absorbed and distributed following oral exposure, but dermal absorption is less efficient. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malathion induces DNA and chromosomal damage in human studies, corroborated by animal and in vitro studies. Bacterial tests were negative. Compelling evidence supports disruption of thyroid and androgen hormone pathways. Hormonal effects (rather than cytotoxicity) may mediate rodent thyroid and mammary gland proliferation. Malaoxon strongly inhibits esterases; atropine ameliorated carcinogenesis-related effects in one study (Cabello et al., 2001). Oxidative stress has been challenged experimentally.

Diazinon has been applied in agriculture and for control of home and garden insects. Production volumes have been relatively low and have reduced further since its restriction in the US and the EU. There is limited evidence in humans for the carcinogenicity of diazinon. Positive associations for NHL, with indications of an exposure-response, were reported by two large multicenter case–control studies (Waddell et al., 2001; McDuffie et al., 2001) and the AHS (Alavanja et al., 2014). Confounding by other pesticides could not explain these findings. An increased leukemia risk reported in several studies was strengthened by a monotonic increase in risk with cumulative diazinon exposure robust to adjustment for other pesticides. Multiple updates from the AHS consistently demonstrated an increased lung cancer risk with an exposure-response association, arguing against a chance finding, with no evidence of confounding by other pesticides, smoking, or other established lung cancer risk factors (Jones et al., 2015). Nonetheless, this finding was not replicated in other populations. Thus, despite positive associations and exposure-response trends for NHL, leukemia and lung cancer, there were few studies and confounding by other pesticides could not be excluded. In rodents, diazinon increased mouse hepatocellular carcinoma and rat leukaemia or lymphoma (combined) incidences, but only in low dose males of each study. Diazinon induced DNA or chromosomal damage in rodents and in human and mammalian cells in vitro. Additional support for human relevance is provided by a positive study of a small number of volunteers exposed to a diazinon formulation (Hatjian et al., 2000). Oxidative stress has been challenged experimentally.

Glyphosate is currently the highest annual global production volume among herbicides (over 700 000 tonnes in 2012), with uses in over 750 different products. A broad-spectrum herbicide, glyphosate is effective against all plant types. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties. Glyphosate has been detected in air during spraying, in water and in food. Population exposure occurs mainly through diet. There is limited evidence in humans for the carcinogenicity of glyphosate, based on a positive association for NHL. Case-control studies in the United States (De Roos et al., 2003), Canada (McDuffie et al., 2001) and Sweden (Hardell et al., 2002; Eriksson et al., 2008) reported increased risks for NHL that persisted after adjustment for exposure to other pesticides. However, the AHS cohort did not show a significant NHL excess (De Roos et al., 2005). Observed increases in multiple myeloma were given less weight

because chance and confounding could not be excluded. In male mice, glyphosate induced a positive trend in renal tubule carcinoma, a rare tumour (EPA, 1986). A second study found increased haemangiosarcoma incidence in male mice (WHO/FAO, 2004). Two rat studies showed increased pancreatic islet cell adenoma incidence in males. A commercial formulation was a skin-tumour promoter in a mouse initiation-promotion study.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. In the rat, glyphosate is distributed and the plasma half-life was >1 day. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection following poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induce DNA and chromosomal damage in mammals and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in community residents after spraying of glyphosate with an adjuvant or of a glyphosate formulation (Bolognesi et al., 2009). Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induce oxidative stress in rodents and in vitro. This mechanism has been challenged experimentally. Glyphosate was classified as Group 2A (probably carcinogenic to humans).

Table: Agents assessed by the Monograph 112 Working Group

Agent	**Activity (Current status)**	**Evidence in humans (Cancer Sites)**	**Evidence in animals**	**Supporting mechanistic evidence***	**Group#**
Tetrachlorvinphos	Insecticide (Banned)	Inadequate	Sufficient		2B
Parathion	Insecticide (Banned)	Inadequate	Sufficient		2B
Malathion	Insecticide (Currently used, high production volume)	Limited (NHL, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A
Diazinon	Insecticide (Banned)	Limited (NHL, leukemia, lung)	Limited	Genotoxicity and oxidative stress	2A

Glyphosate	Herbicide (Currently highest worldwide production volume herbicide)	Limited (NHL)	Sufficient	Genotoxicity and oxidative stress	2A

*Strong evidence and operative in humans; #See IARC preamble for explanation of classification system

References

Alavanja MC, Hofmann JN, Lynch CF et al. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS ONE 2014. 9(10):e109332.

Band PR, Abanto Z, Bert J et al. Prostate cancer risk and exposure to pesticides in British Columbia farmers. Prostate 2011. 71(2):168–83.

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Cabello G, Valenzuela M, Vilaxa A et al. A rat mammary tumor model induced by the organophosphorous pesticides parathion and malathion, possibly through acetylcholinesterase inhibition. Environ Health Perspect 2001. 109(5):471–9.

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Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008. 123(7):1657–63.

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International Agency for Research on Cancer. Volume 112: Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC Working Group. Lyon; 3-10 March 2015. IARC Monogr Eval Carcinog Risk Chem Hum (in press).

Koutros S, Berndt SI, Barry K. Hughes, G. Andreotti, J. A. Hoppin, D. P. Sandler, M. Yeager, L. A. Burdett, J. Yuenger, M. C. Alavanja, and L. E. Beane Freeman. Genetic susceptibility loci, pesticide exposure and prostate cancer risk. PLoS ONE 2013. 8(4):e58195.

McDuffie HH, Pahwa P, McLaughlin JR et al.. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001. 10(11):1155–63.

Mills PK, Yang R, Riordan D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes Control 2005. 16(7):823–30.

NTP. Bioassay of parathion for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser 1979. 70:1–123.

Parker CM, Van Gelder GA, Chai EY, Gellatly JBM, Serota DG, Voelker RW, et al. (1985). Oncogenic evaluation of tetrachlorvinphos in the B6C3F1 mouse. Fundam Appl Toxicol. 5(5):840–54.

Waddell BL, Zahm SH, Baris D et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control 2001. 12(6):509–17.

WHO/FAO (2004). Glyphosate. Pesticides residues in food 2004 Joint FAO/WHO Meeting on Pesticides Residues. Part II Toxicological. IPCS/WHO. 95–162. Available from :[HYPERLINK "http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/"], accessed 6 March 2015.

Margin Info:

Authors

KZ Guyton, D Loomis, Y Grosse, N Guha, L Benbrahim-Tallaa, F El Ghissassi, C Scoccianti, H Mattock and Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France

IARC Monograph Working Group

Members

A Blair (USA) – Meeting Chair
L Fritschi (Australia)
CM Sergi; J McLaughlin (Canada)
GM Calaf (Chile)
F Le Curieux (Finland)
I Baldi (France)
F Forastiere (Italy)
H Kromhout (Netherlands)
A ‘t Mannetje (New Zealand)
T Rodriguez [unable to attend] (Nicaragua)
P Egeghy [unable to attend]; GD Jahnke; CW Jameson; MT Martin; MK Ross; II Rusyn; L Zeise (USA)

Invited Specialists

C Portier (Switzerland)

Representatives

ME Gouze; for the French Agency for Food, Environment and Occupational Health

and Safety, France
J Rowland, U.S. Environmental Protection Agency, USA

Observers

MK Boye Jensen, for Cheminova A/S, Denmark
B Fervers, for the Léon Bérard Centre, France
E Giroux, University Jean-Moulin Lyon 3, France
T Sorahan, for Monsanto Company, USA
C Strupp, for the European Crop Protection Association, Belgium
P Sutton, for the University of California, San Francisco, USA

IARC/WHO Secretariat

L Benbrahim-Tallaa; R Carel; F El Ghissassi; Sonia El-Zaemey; Y Grosse; N Guha, KZ Guyton; C Le Cornet; M Leon; D Loomis; H Mattock; C Scoccianti; A Shapiro, K Straif; J Zavadil

Upcoming meetings

2-9 June 2015, Vol. 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides

6-13 October 2015, Vol. 114: Red Meat and Processed Meat

For more on the IARC Monographs see http://monographs.iarc.fr/

Message

From: Egeghy, Peter [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=49D8224195E64A72882077B1C07940BE-EGEGHY, PETER]
Sent: 11/9/2015 6:21:12 PM
To: Martin, Matt [Martin.Matt@epa.gov]
Subject: FW: IARC Monograph vol 112- EFSA Review of Glyphosate
Attachments: IARCWG112ResponseV2.docx; BFRGlyphosateAddendum.pdf

Importance: High

Hi Matt,
I don't suppose that ORD management would be too keen on either of us singing this "response" letter.
What are your plans?
Thanks,
Peter

-----Original Message-----
From: Chris Portier [mailto:cportier@mac.com]
Sent: Monday, November 09, 2015 6:05 AM
To: Isabelle Baldi <Isabelle.Baldi@isped.u-bordeaux2.fr>; Aaron Blair <blaira@exchange.nih.gov>; GMC24@columbia.edu; Egeghy, Peter <Egeghy.Peter@epa.gov>; Forastiere, Francesco <f.forastiere@deplazio.it>; Lin Fritschi <lin.fritschi@curtin.edu.au>; Jahnke, Gloria (NIH/NIEHS) [E] <jahnke@niehs.nih.gov>; Bill Jameson <drjameson@embarqmail.com>; Kromhout, J. (Hans) <h.kromhout@uu.nl>; frank lecurieux <frank.lecurieux@echa.europa.eu>; Martin, Matt <Martin.Matt@epa.gov>; John McLaughlin <John.McLaughlin@oahpp.ca>; Teresa Rodriguez <Ex. 6 - Personal Privacy> Matthew Ross <MRoss@cvm.msstate.edu>; Rusyn, Ivan <IRusyn@cvm.tamu.edu>; Consolato Sergi <Ex. 6 - Personal Privacy> Mannetje, Andrea <A.Mannetje@massey.ac.nz>; Lauren Zeise <Ex. 6 - Personal Privacy>
Cc: Kate Guyton <GuytonK@iarc.fr>
Subject: IARC Monograph vol 112- EFSA Review of Glyphosate
Importance: High

Dear all,

This week, the European Food Safety Agency (EFSA) will release their reassessment of glyphosate. In this review, they will conclude that glyphosate has no carcinogenic potential. This creates two problems as I see it. The first is that this wekens the strength of the IARC Monograph Program to stimulate change in how some of these agents are reviewed and addressed. The second is that it suggests we did not do our assessment adequately and that, had we seen all of the data they saw, we would have gotten a different answer. I do not intend to let this happen.

The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. This report was drafted prior to the IARC review. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. I have decided to draft a letter that I intend to try to get published in Carcinogenesis that addresses the points made by the BfR in their review. Failing my ability to get this into Carcinogenesis, EHP or some other Journal, I intend to send it as an open letter to the European Commission. I am enclosing both the BfR Addendum and my response for you to look over. I would like as many members of the Working Group to be co-authors on this as possible. If you wish to see changes made to the letter I can certainly work on that. If you are uncomfortable signing on to such a letter, I can appreciate that as in my previous job this would have been impossible. Please let me know by Friday November 13 if you can or cannot join me in this endeavor.

Sincerely,

Christopher Portier

Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 10/24/2017 5:12:28 PM
To: Isabelle Baldi [Isabelle.Baldi@isped.u-bordeaux2.fr]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; Blair, Aaron (NIH/NCI) [V] [blaira@exchange.nih.gov]; Calaf, Gloria [gmc24@cumc.columbia.edu]; Egeghy, Peter [Egeghy.Peter@epa.gov]; f.forastiere@deplazio.it; Lin Fritschi [lin.fritschi@curtin.edu.au]; Jahnke, Gloria (NIH/NIEHS) [E] [jahnke@niehs.nih.gov]; Bill Jameson [drjameson@embarqmail.com]; Kromhout, J. (Hans) [h.kromhout@uu.nl]; frank lecurieux [frank.lecurieux@echa.europa.eu]; john.mclaughlin@oahpp.ca; Teresa Rodriguez Ex. 6 - Personal Privacy Ross, Matthew [MRoss@cvm.msstate.edu]; IRusyn@cvm.tamu.edu; Consolato Sergi Ex. 6 - Personal Privacy Consolato Sergi Ex. 6 - Personal Privacy ; a.mannetje@massey.ac.nz; Lauren Zeise Ex. 6 - Personal Privacy Matthew Martin Ex. 6 - Personal Privacy
CC: Kurt Straif [StraifK@iarc.fr]; Dana Loomis [LoomisD@iarc.fr]; Christopher Portier Ex. 6 - Personal Privacy Patrice Sutton [Patrice.Sutton@ucsf.edu]
Subject: News item, iarc.fr

Dear all,

Kindly be aware that IARC has posted a response to the recent Reuters article:
http://www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php
http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_Response_Reuters_October2017.pdf

With kind regards,
Kate

Kate Z. Guyton, PhD DABT
Scientist, Monographs Section

International Agency for Research on Cancer
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150 cours Albert Thomas
69372 Lyon CEDEX 08, France
Off. +33 472 738 654
E-mail: guytonk@iarc.fr

International Agency for Research on Cancer

World Health Organization

<!--[if !vml]--> *Cancer Research for Cancer Prevention* <!--[endif]-->

Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 9/21/2016 4:42:39 PM
To: Egeghy, Peter [Egeghy.Peter@epa.gov]
CC: Kurt Straif [StraifK@iarc.fr]
Subject: Re: Letter to Vol 112 Working Group

Dear Pete,

Thank you very much for sharing this with us, and for keeping us informed going forward. Please don't hesitate with questions, or if we can be of help.

Kind regards,
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

From: "Egeghy, Peter" <Egeghy.Peter@epa.gov>
Date: Wednesday 21 September 2016 at 14:26
To: Kate Guyton <guytonk@iarc.fr>
Subject: RE: Letter to Vol 112 Working Group

Hi Kate,

I hope you are doing well. Just wanted to let you know that I just received a Freedom of Information Act inquiry from the Free Market Environmental Law Clinic (FME Law) and the Energy & Environment Legal Institute (E&E Legal) requesting the following: "Please provide us, within twenty working days, copies of all email, SameTime and text correspondence, including attachments, which was sent to or from (including also copying, whether as cc: or bcc:), Peter Paul Egeghy in EPA's National Exposure Research Laboratory, Systems Exposure Division, which correspondence include anywhere, whether the body *of the thread* of which it is a part, the Subject, To:, From:, cc:, or bcc: fields a) IARC; b) Lyon, c) "Vol. 112" or any reasonable construct of that (e.g., vol 112, volume 112); and/or d) glyphosate."

I've provided my management with the IARC letter stating that any disclosure of documents or information would be contrary to the privileges and immunities of IARC, and I am waiting to hear back.

Thanks,
Peter

Peter P. Egeghy, Ph.D. M.P.H.

Chief, Human Exposure and Dose Modeling Branch
U.S. Environmental Protection Agency | Office of Research and Development
Mail Drop E205-04 | Research Triangle Park, NC 27711
(919) 541-4103 | egeghy.peter@epa.gov

From: Kathryn Guyton [mailto:GuytonK@iarc.fr]
Sent: Thursday, April 07, 2016 2:38 PM
To: Isabelle Baldi <Isabelle.Baldi@isped.u-bordeaux2.fr>; Blair, Aaron (NIH/NCI) [V] <blaira@exchange.nih.gov>; Blair, Aaron (NIH/NCI) [V] <blaira@exchange.nih.gov>; Calaf, Gloria <gmc24@cumc.columbia.edu>; Egeghy, Peter <Egeghy.Peter@epa.gov>; f.forastiere@deplazio.it; Lin Fritschi <lin.fritschi@curtin.edu.au>; Jahnke, Gloria (NIH/NIEHS) [E] <jahnke@niehs.nih.gov>; Bill Jameson <drjameson@embarqmail.com>; Kromhout, J. (Hans) <h.kromhout@uu.nl>; frank lecurieux <frank.lecurieux@echa.europa.eu>; Martin, Matt <Martin.Matt@epa.gov>; john.mclaughlin@oahpp.ca; Teresa Rodriguez [redacted] Ross, Matthew <MRoss@cvm.msstate.edu>; IRusyn@cvm.tamu.edu; Consolato Sergi <[redacted] Consolato Sergi [redacted] a.mannetje@massey.ac.nz; Lauren Zeise <[redacted]
Cc: Kurt Straif <StraifK@iarc.fr>; Angkana Santhiprechachit <SanthiprechachitA@iarc.fr>
Subject: Letter to Vol 112 Working Group
Importance: High

Dear Vol 112 Working Group members,

Please see the attached letter addressed to your attention.

With best regards,
Kate

Kate Z. Guyton PhD DABT
Responsible Officer, Volume 112
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

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.

Message

From: Kiely, Timothy [Kiely.Timothy@epa.gov]
Sent: 10/19/2015 3:59:16 PM
To: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Suarez, Mark [Suarez.Mark@epa.gov]
CC: Miller, Wynne [Miller.Wynne@epa.gov]; Sims, Diann [Sims.Diann@epa.gov]
Subject: RE: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

Thank you, Yu-Ting. I have a conflict right now.

From: Guilaran, Yu-Ting
Sent: Monday, October 19, 2015 11:20 AM
To: Kiely, Timothy <Kiely.Timothy@epa.gov>; Suarez, Mark <Suarez.Mark@epa.gov>
Cc: Miller, Wynne <Miller.Wynne@epa.gov>; Sims, Diann <Sims.Diann@epa.gov>
Subject: Fwd: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition

I plan to attend and want to see if you are interested in joining. It seems we have only one topic related to the seed treatment...

Sent from my iPhone

Begin forwarded message:

> **From:** "Dinkins, Darlene" <Dinkins.Darlene@epa.gov>
> **Date:** October 19, 2015 at 9:37:11 AM EDT
> **To:** OPP Division Directors & Associate Directors
> <OPP_Division_Directors__Associate_Directors@epa.gov>
> **Subject: Draft Agenda for Thursday's meeting with National Pesticide Reform Coalition**
>
> Good morning,
>
> Please see below the agenda (with topic questions) for the meeting with the National Pesticide Reform Coalition (NGO) on Thursday, October 22, at 1:00 pm. Please let me know who from your staff you would like to invite to the meeting.
>
> *Darlene Dinkins*
> Office of Pesticide Programs
> U.S. Environmental Protection Agency
> (703) 305-5214
>
> ---
>
> **From:** Cynthia Palmer [mailto:CPalmer@abcbirds.org]
> **Sent:** Friday, October 16, 2015 8:54 PM
> **To:** Dinkins, Darlene <Dinkins.Darlene@epa.gov>
> **Subject:** draft agenda for Thursday's meeting
>
> Hi Darlene,
> Here is our draft agenda for Thursday's meeting with OPP leadership.
> Please confirm that I have the correct call-in information for those not able to be there in person.
> Thanks!!
> Have a great weekend.

c.

National Pesticide Reform Coalition (NPRC) Meeting – Draft Agenda
Thursday, 22 October, 2015 at 1 p.m.
EPA - Potomac Yards South, 2777 Crystal Drive, Arlington, VA
Conference line:
Ex. 6 - Personal Privacy

Participants – waiting for others to confirm
American Bird Conservancy – Cynthia Palmer
California Rural Legal Assistance Foundation -- Anne Katten
Center for Biological Diversity -- Brett Hartl
Center for Food Safety – Peter Jenkins and Larissa Walker
Farmworker Association of Florida -- Jeannie Economos
Farmworker Justice -- Virginia Ruiz
Friends of the Earth -- Tiffany Finck-Haynes
Pesticide Action Network -- Emily Marquez
Pollinator Stewardship Council – Michele Colopy and Jeff Anderson
Northwest Center for Alternatives to Pesticides -- Sharon Selvaggio

Neonicotinoids (TFH, LW, PJ, MC, CP)

Many people were surprised when the PPDC Pollinator Subcommittee cancelled this week's meeting due to potential conflicts with NAPPC (North American Pollinator Protection Campaign) and HBHC (Honey Bee Health Coalition), as these represent outside institutions with their own separate agendas. Please explain how this decision came about.

Will the Ninth Circuit Court of Appeals decision on sulfoxaflor change the way other neonics are reviewed by EPA? If so, what changes might we expect for new registrations? For re-registrations?

What other neonics or neonic-like chemicals are coming down the pike for registration?

Please give us the latest estimate as to when we might expect to see the first round of registration review documents for imidacloprid and other neonicotinoids.

There is evidence that the EPA's aquatic reference levels for neonicotinoids are out of line with the science and with those used by other countries. How and when will EPA revise its aquatic benchmarks for the neonicotinoids?

Several new studies and reports raise major concerns about effects of neonicotinoids that EPA may have overlooked, including,

- Williams et al. Honey bee queens highly vulnerable to two neonicotinoid insecticides. *Scientific Reports* 5, Article number: 14621 (2015) doi:10.1038/srep14621
- Botias et al. Neonicotinoid residues in wildflowers, a potential route of chronic exposure for bees. *Environ. Sci. Technol.*, Accepted manuscript • DOI: 10.1021/acs.est.5b03459

- Limay-Rios et al. 2015 Neonicotinoid insecticide residues in soil dust and associated parent soil in fields with a history of seed treatment use on crops in Southwestern Ontario. Environ Toxicol Chem, Accepted manuscript. DOI 10:1002/etc. 3257.
- Center for Food Safety report, *Water Hazard: Aquatic Contamination by Neonicotinoid Insecticides in the United States*," which describes widespread ongoing neonicotinoid contamination in excess of safe levels.

Please indicate whether you will take regulatory action in response to these new indications of serious risks?

Please share with us your current thinking about the matter of re-characterizing neonicotinoid-coated seeds as pesticides under FIFRA, requiring fully enforceable label warnings and use directions for them, instead of exempting the coated seeds as a "treated article."

What progress can you report on EPA's planned completion of its coated seed efficacy assessment for corn and other crops? What is the proposed timeframe for the efficacy analyses on these other commodities? Have EPA plans been affected by the pushback from USDA?

Is EPA planning to remove the 88 active ingredients listed in the EPA document, *Mitigating Exposure from Acutely Toxic Pesticide Products* (docket EPA-HQ-OPP-2014-0818-0003) from all states that do not create State Pollinator Protection Plans?
Nearly all of the formulated products of these actives have bee hazard statements. The EPA action seems to imply that the current "do not apply to blooming crops or weeds if bees are actively visiting the treatment area" label is inadequate protection. This would suggest that all of those pesticides are mis-labeled and that the Administrator should issue a Stop Use Order. There is also a State Primacy issue (FIFRA 405 Chapters 26 and 27). States can receive Primacy if they have adequate laws and ways to enforce those laws; their laws have to be equal to or more stringent than the federal label. Nearly all State plans are based on 24-to-48 hour beekeeper notification, yet no label includes mandatory bee movement requirements. So States that rely on movement for mitigation are reducing protection, something that FIFRA does not allow for.

Incident reporting and biomarkers (CP)
We applaud the efforts underway at EPA to improve its incident reporting systems. But without a biomarker, we will remain in the dark on neonic-related poisonings. We are hoping that the development of biomarkers will go hand in hand with incident reporting upgrades. What progress has been made to develop a biomarker for neonicotinoid poisoning in birds? It should not be difficult to develop a binding assay for brain tissue.

Conazole fungicides (CP)
What are the anticipated timelines for initiating registration review on the conazole fungicides? The official schedule lists these in quarter #1.
We know that the conazole fungicides have interesting reproductive effects in avian species, and yet the field relevance of avian reproductive studies has never really been established (we don't measure the level of residue in the egg so we can't bridge the gap between the laboratory and the wild). We also know that the conazole fungicides are synergistic with other pesticides, especially as regards bee toxicity. How will these characteristics be considered in EPA's registration review?

Rodenticides (CP)
The d-CON settlement of May 30, 2014 halted distribution to retailers as of March 31, 2015. It is troubling to see that brodifacoum-based detail continues to be sold by nearly every major retail outlet.
-Can EPA do anything to get these dangerous products off store shelves?
-Do we have any indication of how much surplus was stockpiled prior to the December 2014 deadline on production?
-What patterns or changes (if any) can you see in the incident data for brodifacoum and other SGARS? For bromethalin or other d-CON replacements?

Herbicides (CP, BH)
Glyphosate, the key ingredient in more than 700 products worldwide, was designated in March as a probable human carcinogen by WHO's International Agency for Research on Cancer. But it appears that the US government has been moving in the other direction on glyphosate: raising the allowable tolerance limits, focusing on weed resistance plans so we can keep using massive amounts, and leaving glyphosate out of the last round of USDA food residue testing.
At our meeting with you last May, we learned that the IARC report will not impact EPA's findings. The IARC used different definitions, dose-response assessments, statistical significance, types of tumors, etc. We were told that EPA looked at the same data and is confident in its separate approach.
Last month, the state of California announced its intention to list glyphosate as a known carcinogen under Proposition 65, which requires the state to publish a list of chemicals that cause cancer, birth defects, or other reproductive harm.
Does the California decision have any bearing on EPA?
What is the expected timeline for EPA's risk assessment on glyphosate?

Likewise, how is the registration review coming along for atrazine? When should we expect to see the risk assessment for atrazine?

MBTA (BH, CP)
Please give us an update on the Migratory Bird Treaty Act MOU between EPA and FWS. Last we heard, the attorneys were "scrubbing it." Any insights on what changes have been made and when it will go into force?

New Avitrol label vs. RED (CP)
At our last meeting, we learned that EPA had just received a proposal from the Avitrol Registrant to address the discrepancy between the RED (Reregistration Eligibility Decision) and the label instructions for elevated sites. What changes have been made?
[Background: The new label for Avitrol (required as of Sept. 22, 2014) does not follow EPA's own directive in the 2007 Reregistration Eligibility Decision for the protection of non-target species. The label encourages users to bait at elevated sites, where feasible. And yet for those elevated applications, and for any uses that are not "in populated areas," the label omits to include the mitigation clearly identified in Table 14 of the RED, namely *that the authorized handler must stay on the site during the entire application period*.]

Worker Protection Standard (VR, JE, AK)
We are glad that EPA is moving forward on WPS implementation and note that cooperative agreements have already been awarded to NASDA Foundation, AFOP and a UC Davis/Oregon

State collaboration. How is EPA going to make sure that these organizations 1) involve farmworker organizations and workers in development of materials and training programs; and 2) develop materials and programs that meet the needs of a workforce that is ethnically and geographically diverse, and working in many different crops?

Advocates have been disappointed by inadequate enforcement of the current WPS, including low penalties and advance notice of inspections. Going forward, how will EPA ensure that new protections (such as those pertaining to minimum age of pesticide handlers, annual safety training, REIs and anti-retaliation) are adequately enforced by states? What steps is EPA taking to monitor state enforcement actions?

International Trade

If ratified, how do the Trans-Pacific and Trans-Atlantic Trade agreements affect EPA autonomy and ability to effectively regulate pesticide use in the US? To what extent do these agreements force the US to follow the lowest-common-denominator approach to pesticide registrations, using the most lax standards of participating nations?

Message

From: Chris Portier [cportier@me.com]
Sent: 6/23/2016 5:54:20 PM
To: Jones, Jim [Jones.Jim@epa.gov]
Subject: Per our brief conversation last night
Attachments: GlyphosateEPA.docx; FiguresandTablesEPA.pptx; ARTIGO META-ANALISE PUBLICADO.pdf; itxc-45-185.pdf; ATT00001.txt; cancer_guidelines_final_3-25-05.pdf; ATT00002.txt; MS Bailer & Portier, 1988, Treatment-induced M.pdf; ATT00003.txt; MS Portier & Bailer, 1989, Survival-Adjusted Q.pdf; ATT00004.txt; PortierHedgesHoel1986.pdf

I include material to be considered by your CARC if they meet again.

C.

Appointment

From: Mojica, Andrea [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F47E2A2BFBC4434AA9CC1E8C2A385DA3-ANDREA MOJICA]
Sent: 11/2/2015 9:11:39 PM
To: Jones, Jim [Jones.Jim@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Mojica, Andrea [Mojica.andrea@epa.gov]; Burke, Thomas [Burke.Thomas@epa.gov]; Gentry, Nathan [Gentry.Nathan@epa.gov]; Smith, Kelley [Smith.Kelley@epa.gov]; Deener, Kathleen [Deener.Kathleen@epa.gov]; Jordan, William [Jordan.William@epa.gov]; Monell, Marty [Monell.Marty@epa.gov]; Vogel, Dana [Vogel.Dana@epa.gov]; Rowland, Jess [Rowland.Jess@epa.gov]; Lowit, Anna [Lowit.Anna@epa.gov]; Smith, Charles [Smith.Charles@epa.gov]; Morton, Thurston [Morton.Thurston@epa.gov]; Perron, Monique [Perron.Monique@epa.gov]; Dunbar, Anwar [Dunbar.Anwar@epa.gov]; Akerman, Gregory [Akerman.Gregory@epa.gov]; Bloem, Thomas [Bloem.Thomas@epa.gov]; Middleton, Karlyn [Middleton.Karlyn@epa.gov]; Jeff Dawson [Dawson.Jeff@epa.gov]; Lobdell, Danelle [Lobdell.Danelle@epa.gov]; Wood, Charles [Wood.Charles@epa.gov]; Nguyen, Thuy [Nguyen.Thuy@epa.gov]; Dix, David [Dix.David@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Rennert, Kevin [Rennert.Kevin@epa.gov]; Cooperstein, Sharon [Cooperstein.Sharon@epa.gov]
CC: Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Venkateshwara, Lata [Venkateshwara.Lata@epa.gov]; Kavlock, Robert [Kavlock.Robert@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]; Jacqueline McQueen [McQueen.Jacqueline@epa.gov]; Birchfield, Norman [Birchfield.Norman@epa.gov]; Cogliano, Vincent [cogliano.vincent@epa.gov]; Martin, Matt [Martin.Matt@epa.gov]; Egeghy, Peter [Egeghy.Peter@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]
BCC: DCRoomRRB41213/ORD [DCRoomRRB41213@epa.gov]

Subject: Glyphosate Human Health meeting
Attachments: glyphosate tom burke briefing slide deck 11 4 15 aftn revised.pptx
Location: DCRoomRRB41213/ORD; call in **Ex. 6 - Personal Privacy**

Start: 11/5/2015 8:00:00 PM
End: 11/5/2015 9:00:00 PM
Show Time As: Busy

glyphosate tom burke briefing sli...

Message

From: Sisco, Debby [Sisco.Debby@epa.gov]
Sent: 10/21/2015 12:04:24 PM
To: Jordan, William [Jordan.William@epa.gov]
Subject: FW: Revised Qs & As for glyphosate
Attachments: Glyphosate - Q and A draft responses 10 19 15 final version.docx

Importance: High

Thought you might want to see these, given some of the questions coming in for the hearing today.

Debby Sisco
Office of Pesticide Programs (7501P)
Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: Ex. 6 - Personal Privacy)

From: Overbey, Dian
Sent: Tuesday, October 20, 2015 10:39 AM
To: Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>
Cc: Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>; Anderson, Neil <Anderson.Neil@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>
Subject: Revised Qs & As for glyphosate
Importance: High

Now internal, with some edits that are highlighted.

Dian D. Overbey
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Potomac Yard S-11238
(703) 305-5018

Message

From: Miller, David [Miller.DavidJ@epa.gov]
Sent: 3/20/2015 9:00:44 PM
To: Jordan, William [Jordan.William@epa.gov]
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)
Attachments: Lancet Onco. Carcinogenicity of tetrachlorvinphos, parathion, malathion....pdf

FYI, per discussion.

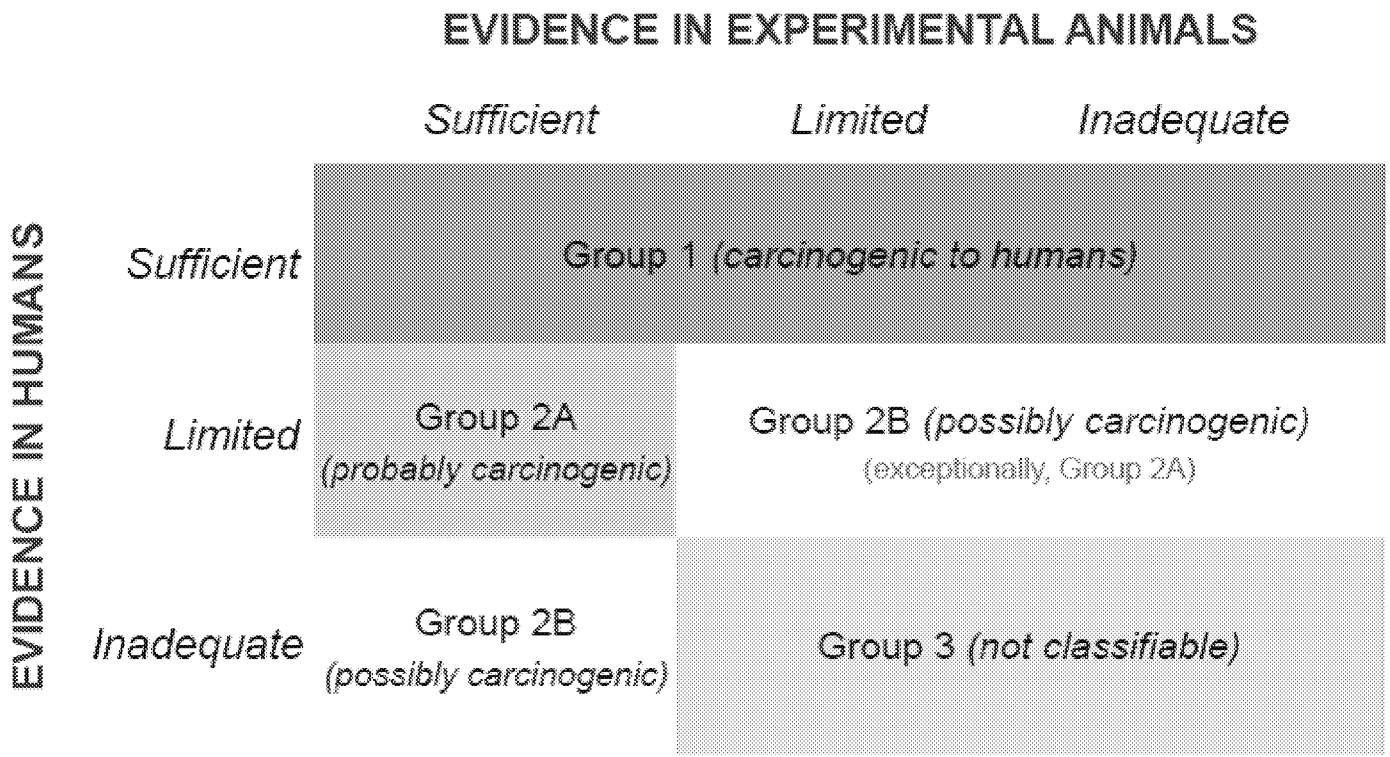
I bet there will be a lot of lights on 'til late tonight at Monsanto HQ in St. Louis.

David.

From: Miller, David
Sent: Friday, March 20, 2015 2:53 PM
To: OPP HED
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)

FYI – for those with an interest, the attached is the recently released IARC summary report on findings for malathion/diazinon/ glyphosate/ tetrachlorpvinphos/parathion.

The WHO/IARC graphic below shows how the 2A (malathion, diazinon, and glyphosate) and 2B (tetrachlorvinphos and parathion) group classifications were derived based on the animal and human epi results reviewed by the IARC Panel.



David

-----Original Message-----
From: Miller, David
Sent: Friday, March 20, 2015 1:57 PM

To: Christensen, Carol; Britton, Wade; Rowland, Jess
Cc: Vogel, Dana
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Thanks, Carol.

I've attached the downloaded PDF of the article to make it simpler for folks.

David.

-----Original Message-----
From: Christensen, Carol
Sent: Friday, March 20, 2015 1:24 PM
To: Britton, Wade; Miller, David; Rowland, Jess
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI: http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf

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From: Christensen, Carol
Sent: Friday, March 20, 2015 11:53 AM
To: Britton, Wade; Miller, David; Rowland, Jess
Subject: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Hi All

I just learned that the summary of the IARC-pesticide meeting is expected to be available on line around 1 pm today. FYI.

I think this is the link: http://www.thelancet.com/journals/lanonc/issue/current.

Carol

Appointment

From: Jones, Tawaunna [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=18CF0CE713464456B2F1219AB61B8558-JONES, TAWA]
Sent: 11/4/2015 7:11:01 PM
To: Jones, Jim [Jones.Jim@epa.gov]; Wise, Louise; Mojica, Andrea; Burke, Thomas; Gentry, Nathan; Smith, Kelley; Deener, Kathleen; Jordan, William; Monell, Marty; Vogel, Dana; Rowland, Jess; Lowit, Anna; Smith, Charles; Morton, Thurston; Perron, Monique; Dunbar, Anwar; Akerman, Gregory; Bloem, Thomas; Middleton, Karlyn; Jeff Dawson; Lobdell, Danelle; Wood, Charles; Nguyen, Thuy; Dix, David
CC: Dinkins, Darlene; Venkateshwara, Lata; Kavlock, Robert; Bahadori, Tina; Fegley, Robert; Jacqueline McQueen; Birchfield, Norman; Cogliano, Vincent

Subject: Glyphosate Human Health meeting
Attachments: glyphosate tom burke briefing slide deck 11 4 15 aftn revised.pptx
Location: DCRoomRRB41213/ORD; call in Ex. 6 - Personal Privacy

Start: 11/5/2015 8:00:00 PM
End: 11/5/2015 9:00:00 PM
Show Time As: Tentative

glyphosate tom burke briefing sli...

Message

From: Martyn Smith [martynts@berkeley.edu]
Sent: 11/24/2015 10:10:14 PM
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; 'Chris Portier' [Ex. 6 - Personal Privacy]; Gibbons, Catherine [Gibbons.Catherine@epa.gov]; 'Kate Guyton' [GuytonK@iarc.fr]; lambert@oncology.wisc.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
Attachments: 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

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

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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NIH National Institute of Environmental Health Sciences

Environ Health Perspect DOI: 10.1289/ehp.1509912
Advance Publication: Not Copyedited

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

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Running title: Characteristic properties of human carcinogens

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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.

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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.

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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.

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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

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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).

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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

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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.

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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.

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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

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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

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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.

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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.

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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

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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

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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

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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

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encompass a range of non-cancer toxicities, "top-down" broad literature searches aimed at comprehensively identifying studies on all potential toxic effects of an agent are employed (EPA 2014; NRC 2014). These comprehensive searches of peer-reviewed literature are supplemented by examining past IARC Monographs or other authoritative reviews; databases (e.g., PubChem); and, peer-reviewed government reports can also be systematically searched. The search terms used and literature retrieved can be documented (e.g., using MyNCBI, which saves searches of the National Center for Biotechnology database, or https://hawcproject.org).

Step 2: Screening and organizing the results

Based on title and abstract review, studies identified initially are excluded if no data on the chemical or a metabolite are reported, or if no data on toxicological or other cancer-related effects of the chemical is provided. For example, a study on levels of a chemical, but not effects of the chemical, would be excluded. Included studies are then organized by the population (human or experimental systems) and by the endpoints associated with the 10 key characteristics (see Table 1). Studies relevant to toxicokinetics (covering absorption, distribution, metabolism and excretion) are also identified. Additionally, authoritative, comprehensive review articles are identified, as are studies reporting toxicological endpoints in cancer target and non-target tissues. These may include morphological evaluations pertaining to the dysfunction of organs, tissues, and cells. Importantly, studies reporting endpoints that are relevant to multiple characteristics may fall under several categories.

To illustrate these two steps, targeted literature searches were conducted to identify endpoints for the effects of benzene pertinent to the 10 key characteristics, in populations comprising humans or experimental systems. The literature searches were conducted using the Health Assessment

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Workplace Collaborative (HAWC) Literature Search tool (https://hawcproject.org/), documenting the search terms, sources, and articles retrieved. Following title and abstract review, studies were excluded if they were not about benzene or its metabolites, or if they reported no data on toxicological endpoints. Included studies were further sorted into categories representing the 10 key characteristics based on the mechanistic endpoints and species evaluated (i.e. human in vivo, human in vitro, mammalian in vivo, mammalian in vitro, non-mammalian; see Figure 1). The figure also identifies reviews, gene expression studies, and articles relevant to toxicokinetics, toxicity, or susceptibility.

Step 3: Using the key characteristics to synthesize mechanistic information and to develop adverse-outcome networks

It is increasingly evident that multiple biological alterations or sets of different perturbations are necessary to convert a normal cell to a transformed cell and ultimately a tumor (Hanahan and Weinberg 2011). Carcinogens appear to impact this complex process in various ways and can act through multiple mechanisms to induce cancer and other adverse health outcomes (Goodson et al. 2015; Guyton et al. 2009). Using the 10 key characteristics as a basis, the collected information can be organized to form hypotheses and evaluate the evidentiary support for mechanistic events as a function of relevant aspects (e.g. dose, species, temporality, etc) (Guyton et al. 2009). The diverse and complex mechanistic endpoints elicited by benzene can then be organized into an overview inclusive of multiple alterations and any linkages thereof (Figure 2). The resulting overview can provide guidance for further assessments of the literature, including dose relevance, species relevance, and temporality of events. This additional detailed information can then be used to produce proposed mechanisms or adverse outcome pathway networks as

described in (McHale et al. 2012) and the EPA's NexGen Risk Assessment Report (EPA 2014). We note that there is evidence that benzene is associated with 8 of the 10 key characteristics we have described.

Figure 3 presents a similar overview for PCBs based on data from IARC Monograph Volume 107 (IARC 2015). In summarizing the mechanistic evidence, this Monograph Working Group indicated that PCBs may induce up to 7 of the 10 key characteristics in producing carcinogenicity (Lauby-Secretan et al. 2013). We note that the less chlorinated PCBs are associated with key characteristics similar to benzene (metabolic activation, DNA damage, cellular proliferation), whereas the dioxin-like PCBs are associated primarily with receptor-mediated activities.

Recently, using this same approach, the Working Groups of IARC Monograph Volume 112 and Volume 113 concluded that strong mechanistic evidence exists for 5 key characteristics being involved in malathion carcinogenicity (i.e. genotoxicity, oxidative stress, inflammation, receptor-mediated effects and cell proliferation or death), 3 in DDT carcinogenicity (i.e. immunosuppression, receptor-mediated effects and oxidative stress) and 2 each for diazinon and glyphosate (i.e. genotoxicity and oxidative stress), providing evidence to support their classification as probable human carcinogens in Group 2A (Guyton et al. 2015; Loomis et al. 2015).

Discussion and Conclusions

Identification and incorporation of important, novel scientific findings providing insights into cancer mechanisms is an increasingly essential aspect of carcinogen hazard identification and

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risk assessment. Systematic approaches are needed to organize the available mechanistic data relevant to the overall evaluation of the carcinogenic hazard of an agent. Information to support the identification of 10 key characteristics of human carcinogens was obtained during the Volume 100 Monographs and two subsequent expert workshops. These characteristics, although not necessarily representing mechanisms themselves, provide the rationale for an objective approach to identifying and organizing relevant mechanistic data. Using literature collected previously by others as well as by us, we have categorized the literature data according to the 10 characteristics for benzene and PCBs. This approach identified pertinent positive literature for 8 of the 10 key characteristics on benzene and 7 for PCBs, thereby providing a practical, objective method for organizing the large mechanistic literature associated with these chemicals.

This approach also lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications. In the IARC Monographs the strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated using the terms 'weak', 'moderate' or 'strong' (http://monographs.iarc.fr/ENG/Preamble/index.php). In general, the strongest indications that a particular mechanism operates in humans derive from data obtained in exposed humans or in human cells in vitro. Data from experimental animals can support a mechanism by findings of consistent results and from studies that challenge the hypothesized mechanism experimentally. Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumors observed in experimental animals

are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favored mechanism. All of these factors make assignment of descriptors such as 'strong' to the mechanistic evidence challenging, but recent experience with two IARC Monograph meetings suggest that the weighing of the evidence on the basis of the 10 key characteristics focuses the group discussion on the available science and allows rapid consensus to be reached regardless of the strength of the evidence base (Guyton et al. 2015; Loomis et al. 2015).

Because the literature search and categorization approach described herein is comprehensive, it may aid consideration of the overall strength of the mechanistic database according to these principles. In particular, it is inclusive of diverse mechanistic evidence, enabling support for divergent or related mechanisms from human and experimental systems to be identified. Moreover, the literature support for endpoints relevant to specific mechanisms can be evaluated in an integrated fashion when the mechanism is complex. Additionally, comparisons across agents will be facilitated, including evaluation of any similarities or differences in the pattern of key characteristics with agents that are currently classified.

As this approach is carried forward, we hope it will facilitate the objective identification of mechanistic data for consideration in the context of epidemiology, animal bioassay, or other types of evidence (e.g., studies in model organisms or *in vitro* assays) when classifying agents with regard to carcinogenic hazard. Equally important is to consider whether key characteristics of carcinogens are apparent upon exposures that are relevant to human health (Thomas et al. 2013). Overall, these developments will aid advancement of future evaluations of newly

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introduced chemicals, including those for which mechanistic data provide the primary evidence of carcinogenicity.

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REFERENCES

Allday MJ. 2013. Ebv finds a polycomb-mediated, epigenetic solution to the problem of oncogenic stress responses triggered by infection. Frontiers in genetics 4:212.

Arana ME, Kunkel TA. 2010. Mutator phenotypes due to DNA replication infidelity. Semin Cancer Biol 20:304-311.

Aranda A, Pascual A. 2001. Nuclear hormone receptors and gene expression. Physiological reviews 81:1269-1304.

Baek SH, Kim KI. 2014. Emerging roles of orphan nuclear receptors in cancer. Annual review of physiology 76:177-195.

Batal M, Boudry I, Mouret S, Clery-Barraud C, Wartelle J, Berard I, et al. 2014. DNA damage in internal organs after cutaneous exposure to sulphur mustard. Toxicology and applied pharmacology 278:39-44.

Berquist BR, Wilson DM, 3rd. 2012. Pathways for repairing and tolerating the spectrum of oxidative DNA lesions. Cancer Lett 327:61-72.

Bhattacharjee P, Banerjee M, Giri AK. 2013. Role of genomic instability in arsenic-induced carcinogenicity. A review. Environment international 53:29-40.

Bielas JH, Loeb KR, Rubin BP, True LD, Loeb LA. 2006. Human cancers express a mutator phenotype. Proc Natl Acad Sci U S A 103:18238-18242.

Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. 2009. A review of human carcinogens--part b: Biological agents. The Lancet Oncology 10:321-322.

Candeias S, Pons B, Viau M, Caillat S, Sauvaigo S. 2010. Direct inhibition of excision/synthesis DNA repair activities by cadmium: Analysis on dedicated biochips. Mutat Res 694:53-59.

Chen SH, Oyarzabal EA, Hong JS. 2015. Critical role of the mac1/nox2 pathway in mediating reactive microgliosis-generated chronic neuroinflammation and progressive neurodegeneration. Current opinion in pharmacology 26:54-60.

Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. 2011. Preventable exposures associated with human cancers. Journal of the National Cancer Institute 103:1827-1839.

Coussens LM, Pollard JW. 2011. Leukocytes in mammary development and cancer. Cold Spring Harbor perspectives in biology 3.

Coussens LM, Zitvogel L, Palucka AK. 2013. Neutralizing tumor-promoting chronic inflammation: A magic bullet? Science 339:286-291.

Ehrenberg L. 1984. Covalent binding of genotoxic agents to proteins and nucleic acids. IARC scientific publications:107-114.

Ehrenberg L, P. Brooks, H. Druckrey, B. Langerlöf, J. Litwin, G. Williams 1973. Report of group 3. Vol. 3:AMBIO Special Report, 15-16.

EPA US. 2014. Next generation risk assessment: Incorporation of recent advances in molecular, computational, and systems biology. EPA/600/R-14/004. Washington, DC:U.S. Environmental Protection Agency.

Figueira TR, Barros MH, Camargo AA, Castilho RF, Ferreira JC, Kowaltowski AJ, et al. 2013. Mitochondria as a source of reactive oxygen and nitrogen species: From molecular mechanisms to human health. Antioxidants & redox signaling 18:2029-2074.

Filipic M. 2012. Mechanisms of cadmium induced genomic instability. Mutat Res 733:69-77.

Galluzzi L, Bravo-San Pedro JM, Vitale I, Aaronson SA, Abrams JM, Adam D, et al. 2015. Essential versus accessory aspects of cell death: Recommendations of the nccd 2015. Cell death and differentiation 22:58-73.

Goodson WH, 3rd, Lowe L, Carpenter DO, Gilbertson M, Manaf Ali A, Lopez de Cerain Salsamendi A, et al. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: The challenge ahead. Carcinogenesis 36 Suppl 1:S254-296.

Griner EM, Kazanietz MG. 2007. Protein kinase c and other diacylglycerol effectors in cancer. Nature reviews Cancer 7:281-294.

Grivennikov SI, Greten FR, Karin M. 2010. Immunity, inflammation, and cancer. Cell 140:883-899.

Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. 2007. Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. The Lancet Oncology 8:679-680.

Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, et al. 2009. Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. Mutat Res 681:230-240.

Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, et al. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology 16:490-491.

Hanahan D, Weinberg RA. 2011. Hallmarks of cancer: The next generation. Cell 144:646-674.

Harris CC. 2015. Cause and prevention of human cancer. Carcinogenesis 36 Suppl 1:S1.

Hartge P, Smith MT. 2007. Environmental and behavioral factors and the risk of non-hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 16:367-368.

Hecht SS. 2012. Lung carcinogenesis by tobacco smoke. Int J Cancer 131:2724-2732.

Herceg Z, Lambert MP, van Veldhoven K, Demetriou C, Vineis P, Smith MT, et al. 2013. Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation. Carcinogenesis 34:1955-1967.

Higgins JPT, Green S. 2011. Cochrane handbook for systematic reviews of interventions, version 5.1.0. .

Hu Z, Brooks SA, Dormoy V, Hsu CW, Hsu HY, Lin LT, et al. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: Focus on the cancer hallmark of tumor angiogenesis. Carcinogenesis 36 Suppl 1:S184-202.

IARC. 2008. Iarc monographs on the evaluation of carcinogenic risks to humans. Volume 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer 97:3-471.

Kadhim M, Salomaa S, Wright E, Hildebrandt G, Belyakov OV, Prise KM, et al. 2013. Non-targeted effects of ionising radiation-implications for low dose risk. Mutat Res 752:84-98.

Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, et al. 2015. Diabetic cardiovascular disease induced by oxidative stress. International journal of molecular sciences 16:25234-25263.

Klaunig JE, Wang Z, Pu X, Zhou S. 2011. Oxidative stress and oxidative damage in chemical carcinogenesis. Toxicology and applied pharmacology 254:86-99.

Klingelhutz AJ. 1999. The roles of telomeres and telomerase in cellular immortalization and the development of cancer. Anticancer research 19:4823-4830.

Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, et al. 2014. The navigation guide - evidence-based medicine meets environmental health: Systematic review of nonhuman evidence for pfoa effects on fetal growth. Environ Health Perspect 122:1015-1027.

Kushman ME, Kraft AD, Guyton KZ, Chiu WA, Makris SL, Rusyn I. 2013. A systematic approach for identifying and presenting mechanistic evidence in human health assessments. Regulatory toxicology and pharmacology : RTP 67:266-277.

Lauby-Secretan B, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. 2013. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. The Lancet Oncology 14:287-288.

Loomis D, Guyton K, Grosse Y, El Ghissasi F, Bouvard V, Benbrahim-Tallaa L, et al. 2015. Carcinogenicity of lindane, ddt, and 2,4-dichlorophenoxyacetic acid. The Lancet Oncology.

Luch A, Frey FC, Meier R, Fei J, Naegeli H. 2014. Low-dose formaldehyde delays DNA damage recognition and DNA excision repair in human cells. PloS one 9:e94149.

Ma Q. 2011. Influence of light on aryl hydrocarbon receptor signaling and consequences in drug metabolism, physiology and disease. Expert opinion on drug metabolism & toxicology 7:1267-1293.

McHale CM, Zhang L, Smith MT. 2012. Current understanding of the mechanism of benzene-induced leukemia in humans: Implications for risk assessment. Carcinogenesis 33:240-252.

Miller JA. 1970. Carcinogenesis by chemicals: An overview--g. H. A. Clowes memorial lecture. Cancer Res 30:559-576.

Multhoff G, Radons J. 2012. Radiation, inflammation, and immune responses in cancer. Front Oncol 2:58.

NRC. 2014. Review of epa's integrated risk information system (iris) process. Washington, DC:National Research Council.

O'Brien PJ. 2000. Peroxidases. Chem Biol Interact 129:113-139.

Pogribny IP, Rusyn I. 2013. Environmental toxicants, epigenetics, and cancer. Advances in experimental medicine and biology 754:215-232.

Pollard JW. 2008. Macrophages define the invasive microenvironment in breast cancer. Journal of leukocyte biology 84:623-630.

Preston BD, Albertson TM, Herr AJ. 2010. DNA replication fidelity and cancer. Semin Cancer Biol 20:281-293.

Rafferty P, Egenolf D, Brosnan K, Makropoulos D, Jordan J, Meshaw K, et al. 2012. Immunotoxicologic effects of cyclosporine on tumor progression in models of squamous cell carcinoma and b-cell lymphoma in c3h mice. Journal of immunotoxicology 9:43-55.

Rajendran JG, Mankoff DA, O'Sullivan F, Peterson LM, Schwartz DL, Conrad EU, et al. 2004. Hypoxia and glucose metabolism in malignant tumors: Evaluation by [18f]fluoromisonidazole and [18f]fluorodeoxyglucose positron emission tomography imaging. Clinical cancer research : an official journal of the American Association for Cancer Research 10:2245-2252.

Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122:711-718.

Rushmore TH, Kong AN. 2002. Pharmacogenomics, regulation and signaling pathways of phase i and ii drug metabolizing enzymes. Current drug metabolism 3:481-490.

Rusyn I, Asakura S, Li Y, Kosyk O, Koc H, Nakamura J, et al. 2005. Effects of ethylene oxide and ethylene inhalation on DNA adducts, apurinic/apyrimidinic sites and expression of base excision DNA repair genes in rat brain, spleen, and liver. DNA repair 4:1099-1110.

Ryter SW, Mizumura K, Choi AM. 2014. The impact of autophagy on cell death modalities. International journal of cell biology 2014:502676.

Saha A, Kaul R, Murakami M, Robertson ES. 2010. Tumor viruses and cancer biology: Modulating signaling pathways for therapeutic intervention. Cancer biology & therapy 10:961-978.

Salnikow K, Zhitkovich A. 2008. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: Nickel, arsenic, and chromium. Chemical research in toxicology 21:28-44.

Shaughnessy DT, DeMarini, D. M. . 2009. Types and consequences of DNA damage. In: Chemoprevention of cancer and DNA damage by dietary factors, (S. Knasmüller DMD, I. Johnson and C. Gerhäuser, ed). Weinheim, Germany:Wiley-VCH Verlag GmbH & Co. KGaA.

Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJ. 1980. Multistage chemical carcinogenesis in mouse skin. Current problems in dermatology 10:193-218.

Smith MT. 1996. The mechanism of benzene-induced leukemia: A hypothesis and speculations on the causes of leukemia. Environ Health Perspect 104 Suppl 6:1219-1225.

Smith MT, Skibola CF, Allan JM, Morgan GJ. 2004. Causal models of leukaemia and lymphoma. IARC scientific publications:373-392.

Suman S, Sharma PK, Rai G, Mishra S, Arora D, Gupta P, et al. 2015. Current perspectives of molecular pathways involved in chronic inflammation-mediated breast cancer. Biochemical and biophysical research communications.

Thomas RS, Philbert MA, Auerbach SS, Wetmore BA, Devito MJ, Cote I, et al. 2013. Incorporating new technologies into toxicity testing and risk assessment: Moving from 21st century vision to a data-driven framework. Toxicological sciences : an official journal of the Society of Toxicology 136:4-18.

Trinchieri G. 2012. Cancer and inflammation: An old intuition with rapidly evolving new concepts. Annu Rev Immunol 30:677-706.

Wallace BD, Redinbo MR. 2013. Xenobiotic-sensing nuclear receptors involved in drug metabolism: A structural perspective. Drug metabolism reviews 45:79-100.

Yugawa T, Kiyono T. 2009. Molecular mechanisms of cervical carcinogenesis by high-risk human papillomaviruses: Novel functions of e6 and e7 oncoproteins. Reviews in medical virology 19:97-113.

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Table 1. Key characteristics of carcinogens.

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)
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
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

Any of the 10 characteristics in this table could interact with any other (e.g. oxidative stress, DNA damage and chronic inflammation, which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone).

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Figure Legends

Figure 1: Literature flow diagram, illustrating the systematic identification and categorization process for benzene mechanistic studies. Using appropriate MeSH terms and key words, targeted literature searches were conducted for the 10 key characteristics using online tools available from the HAWC Project (https://hawcproject.org/). Section 4 refers to the location of the discussion of mechanistic data within the IARC Monograph structure (http://monographs.iarc.fr/ENG/Preamble/currentb4studiesother0706.php). All inclusion categories were expanded to document the number of studies attributed to each, down to the individual key characteristic level, which were expanded to illustrate human information when >100 total studies were identified. Less frequently encountered key characteristic categories (grey circles) were left unexpanded for clarity. Human refers to both humans exposed in vivo and human cells exposed in vitro.

Figure 2: An overview of how benzene induces 8 of the key characteristics in a probable mechanism of carcinogenicity. A full review of these mechanistic data is given in (McHale et al. 2012), from which this Figure was adapted.

Figure 3: An overview of how polychlorinated biphenyls (PCBs) may induce 7 key characteristics in their carcinogenicity (Lauby-Secretan et al. 2013). Highly chlorinated PCBs act as ligands for the aryl hydrocarbon receptor (AhR) and other receptors activating a large number of genes in a tissue- and cell-specific manner that can lead to cell proliferation, apoptosis and other effects that influence cancer risk. Less chlorinated PCBs can be activated to electrophilic metabolites, such as arene oxides and quinones, which can cause genotoxic effects and induce oxidative stress. Receptor binding to CAR and AhR (a key characteristic) leads

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xenobiotic metabolism induction (not a key characteristic, brown not blue box) that in turn leads to genotoxicity and other key characteristics.

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Figure 1

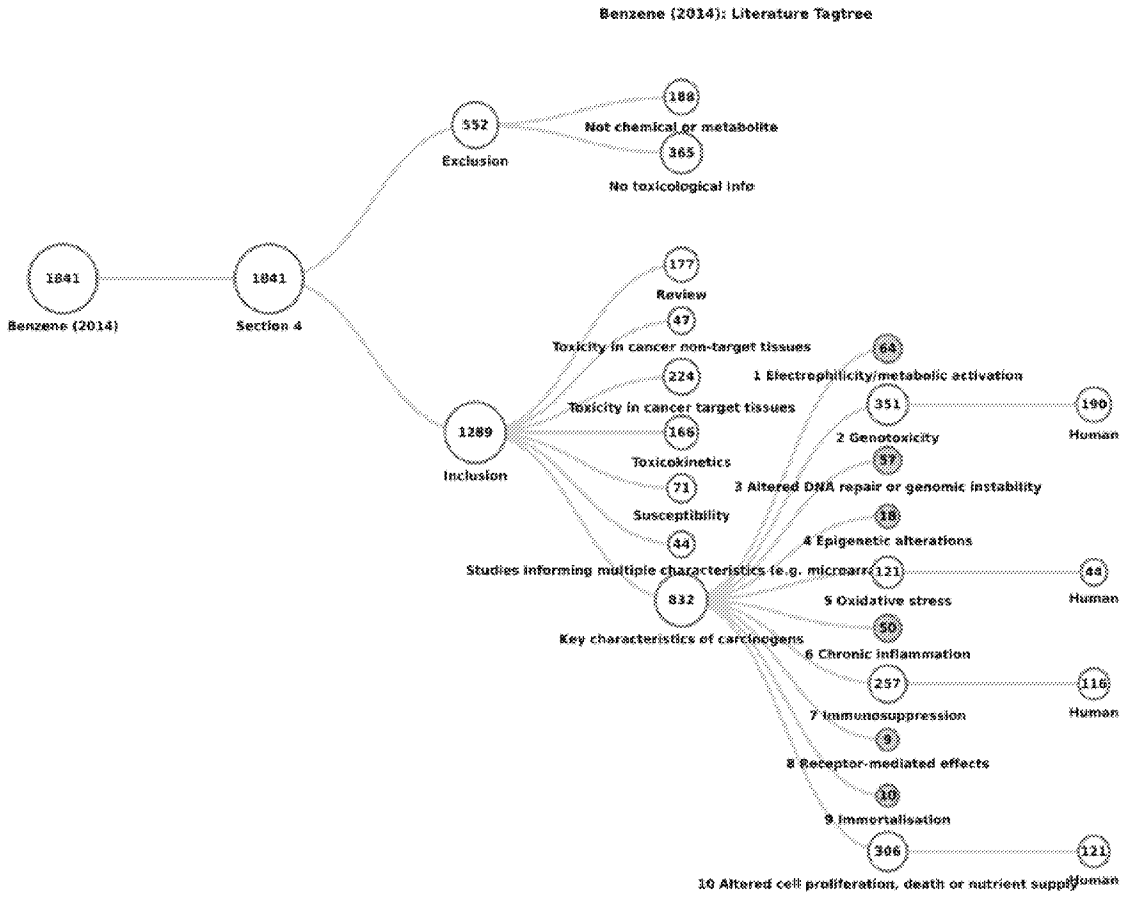

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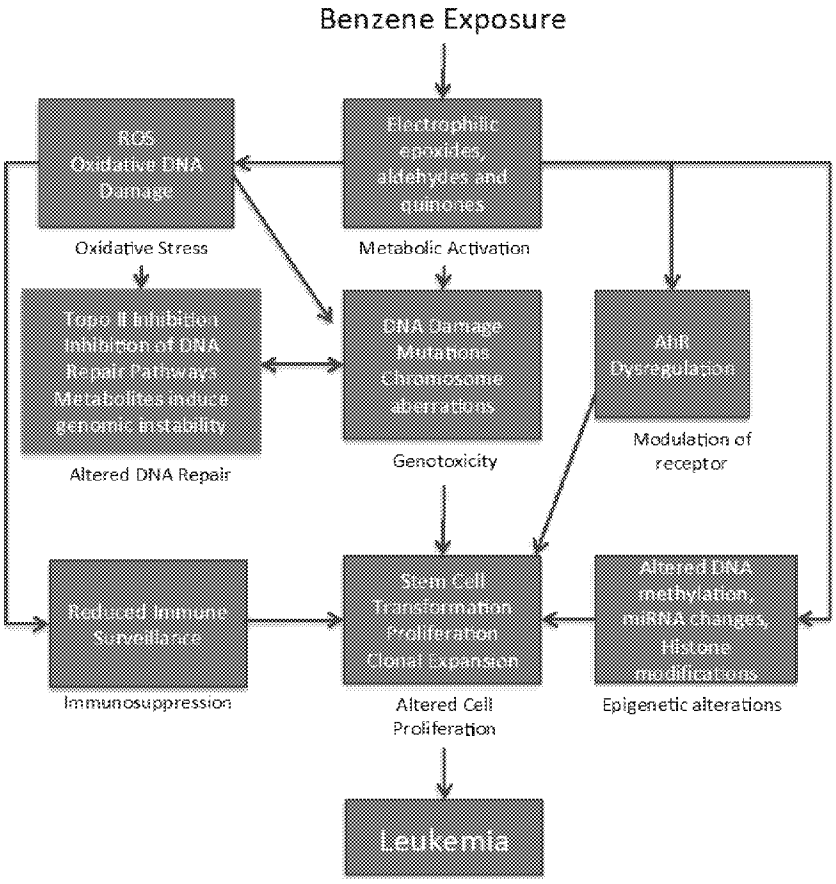
Figure 2



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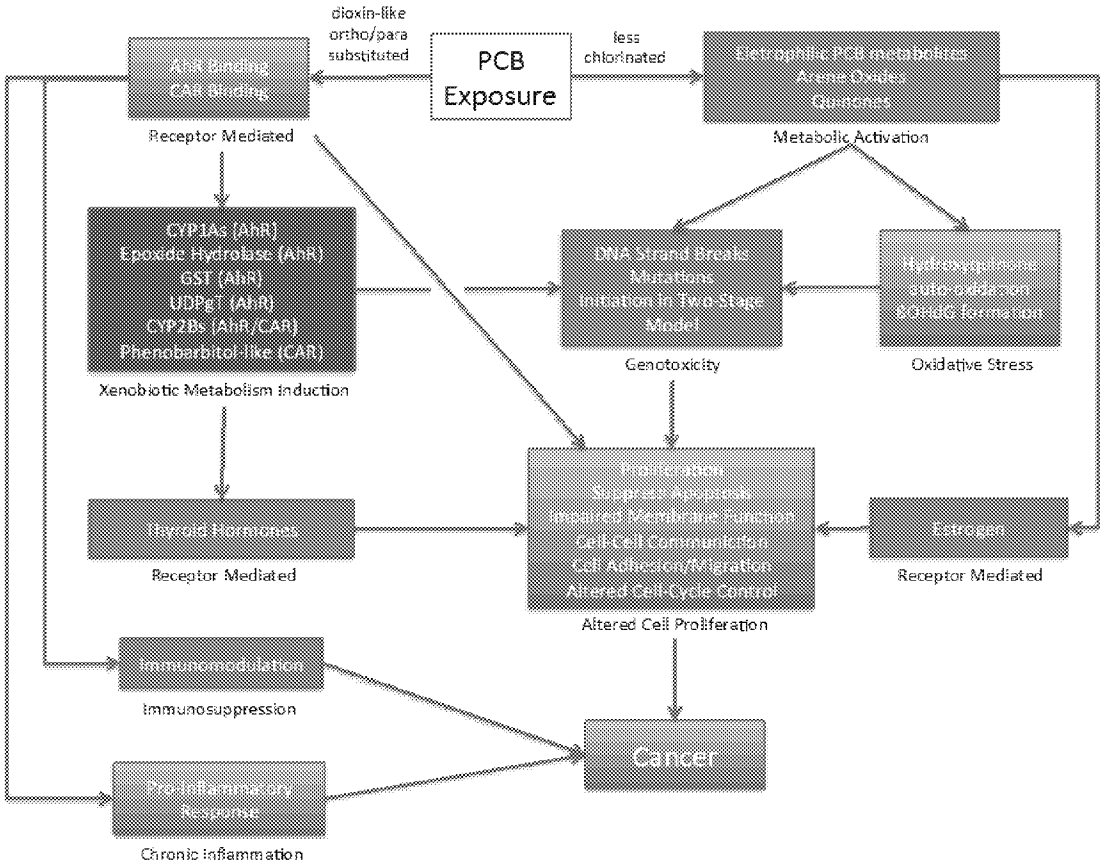
Figure 3