Message

From: HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]
Sent: 3/18/2015 12:52:38 PM
To: VICINI, JOHN L [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=56908]; FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=180070]
Subject: RE: IARC Outcomes, Process, and Response

That's a lot of fuzz balls scurrying around cages.... I would add the word 'little', but the rats can get up to a kilo by the end of the study – in my lab days we used to call them "Polar Bear Rats"!

From: VICINI, JOHN L [AG/1000]
Sent: Wednesday, March 18, 2015 7:49 AM
To: HEYDENS, WILLIAM F [AG/1000]; FARMER, DONNA R [AG/1000]
Subject: RE: IARC Outcomes, Process, and Response

The more the merrier!

From: HEYDENS, WILLIAM F [AG/1000]
Sent: Wednesday, March 18, 2015 7:47 AM
To: VICINI, JOHN L [AG/1000]; FARMER, DONNA R [AG/1000]
Subject: RE: IARC Outcomes, Process, and Response

Per our publication, the complete breakout (total 14 studies) is

From: HEYDENS, WILLIAM F [AG/1000]
Sent: Wednesday, March 18, 2015 7:39 AM
To: VICINI, JOHN L [AG/1000]; FARMER, DONNA R [AG/1000]
Subject: RE: IARC Outcomes, Process, and Response

I don't know the publication date but the companies with chronic data are:

1. Monsanto (obviously) – rat (2) & mouse
2. Cheminova – rat & mouse
3. Feinchemie Schwebda – rat & mouse
4. Excel - rat
5. Syngenta – rat
6. Nufarm – rat & mouse
7. Arysta – rat & mouse

And there was a 2-year study in Wistar rats from academic researchers in Poland (Chruscielska et al, 2000) which was included in our review publication).

From: VICINI, JOHN L [AG/1000]
Sent: Wednesday, March 18, 2015 7:04 AM
To: FARMER, DONNA R [AG/1000]; HEYDENS, WILLIAM F [AG/1000]
Subject: RE: IARC Outcomes, Process, and Response

Thanks. I can check with David. I thought you might just know without looking it up.

Melissa wants some technical talking points that I'm starting to do. Do you guys think that the Lancet paper is that last half of section 5?

From: FARMER, DONNA R [AG/1000]
Sent: Wednesday, March 18, 2015 6:56 AM
To: VICINI, JOHN L [AG/1000]; HEYDENS, WILLIAM F [AG/1000]
Subject: RE: IARC Outcomes, Process, and Response

http://www.erigone.com/EU-Regulation/renewal-existing-a-s.htm

I believe the submission was 5/12 and I need to confirm with David the names of the companies with the 6 data sets.

Miller is talking about multiple myeloma this was the DeRoos 2005 but Lash (2007) and Sorahan's 2015 publication which he is quoting show this was due to restricted data set so IARC did agree with that and concluded no association with multiple myeloma but said there was with NHL – I would have him use the DeRoos 2005 paper no findings overall with any cancer including NHL (only the restricted data set for multiple myeloma) and the Freeman 2009 paper – no cancer associated with glyphosate (a review of the NHL cancer findings up to 2009) both AHS publications. See why this is so unbelievable that Aaron Blair would not defend his very own AHS?

From: VICINI, JOHN L [AG/1000]
Sent: Tuesday, March 17, 2015 10:16 PM
To: HEYDENS, WILLIAM F [AG/1000]; FARMER, DONNA R [AG/1000]
Subject: Fwd: IARC Outcomes, Process, and Response

Can one of you help with the x's in the attached file.

Begin forwarded message:
From: "SACHS, ERIC S [AG/1000]" [redacted]
Date: March 17, 2015 at 8:58:41 PM CDT
To: "VICINI, JOHN L [AG/1000]" [redacted] "REYNOLDS, TRACEY L [AG/1000]" [redacted], "HOOD, AIMEE [AG/1000]" [redacted]
Subject: Fwd: IARC Outcomes, Process, and Response

John

Please fill in the missing information then I will send back to Henry. When should he post? Do you want him to break the embargo? If so, we need to ask him.

Eric

Sent from my iPhone

Begin forwarded message:
From: Henry Miller [redacted]
Date: March 17, 2015 at 7:06:22 PM CDT
To: "ERIC S SACHS [AG/1000]" [redacted]
Subject: Re: IARC Outcomes, Process, and Response
Reply-To: Henry Miller [redacted]

Back to you.

As always, accuracy is paramount, but all comments are welcome.

From: "ERIC S SACHS [AG/1000]" <[redacted]
To: "Henry Miller" <[redacted]
Sent: Tuesday, March 17, 2015 3:22:58 PM
Subject: RE: IARC Outcomes, Process, and Response

Here is our draft...still quite rough...but a good start for your magic. It got category 2A!

Eric

From: Henry Miller [[redacted]
Sent: Tuesday, March 17, 2015 3:10 PM
To: SACHS, ERIC S [AG/1000]
Subject: Re: IARC Outcomes, Process, and Response

In the meantime, you're keeping me in suspense. What was the outcome?

From: "ERIC S SACHS [AG/1000]" <[redacted]>
To: "Henry Miller" <[redacted]@[redacted]
Sent: Tuesday, March 17, 2015 10:23:03 AM
Subject: RE: IARC Outcomes, Process, and Response

We have a draft nearly done and will send to you by tomorrow.

Eric

From: Henry Miller [redacted]
Sent: Thursday, March 12, 2015 12:46 PM
To: SACHS, ERIC S [AG/1000]
Subject: Re: IARC Outcomes, Process, and Response

I would be if I could start from a high-quality draft. I'm absolutely inundated with projects right now.

From: "ERIC S SACHS [AG/1000]" <[redacted]@[redacted]
To: "Henry Miller" <[redacted]@[redacted]
Sent: Thursday, March 12, 2015 10:28:53 AM
Subject: IARC Outcomes, Process, and Response

Henry,

Are you interested in writing more on the topic of the IARC panel, its process and controversial decision? I have background and can provide information if needed. The outcome is embargoed but will be communicated as early as next week.

Eric

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Henry I. Miller, M.D.
Robert Wesson Fellow in Scientific Philosophy & Public Policy
Hoover Institution | Stanford University

Stanford, CA [redacted]

U.S.A.
Phone: [redacted]

Email: [redacted]

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Henry I. Miller, M.D.
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Henry I. Miller, M.D.
Robert Wesson Fellow in Scientific Philosophy
& Public Policy
Hoover Institution | Stanford University

Stanford, CA [redacted]

[redacted]

March 17, 2015

March Madness from the United Nations

Henry I. Miller

The NCAA basketball tournament has started and I hope I pick my brackets as well as I predicted the outcome of this month's meeting of the International Agency for Research on Cancer (IARC), a component of the UN's World Health Organization. It always pays to bet against a United Nations agency getting things right, and this conclave was no exception.

For the first time since 1991, the focus of this IARC review was on pesticides. At this meeting, five pesticides were evaluated and three of them were classified as "probably carcinogenic." But the U.S. EPA had previously given each of these three active ingredients favorable safety classifications regarding carcinogenic potential. Why the differences?

The obvious reason would be new, game-changing data. But there wasn't any. The disparity appears to be that IARC bases their conclusion on potential *hazard* rather than the actual risk of harm. What does that mean to you and me? Well, we participate in hazardous activities everyday that have the potential to harm us–we use knives, drive a car, fly on an airplane or walk down stairs. However, the risk--the probability that we will actually be harmed-- associated with each of these activities is low.

The same applies to the IARC's analysis of glyphosate. The data (and a selected set of data, at that) were reviewed to determine whether glyphosate is capable of causing cancer. As with common chemicals like sugar, salt and water, and foods like nutmeg and licorice, glyphosate at very high doses is capable of causing harm to humans. That's what the IARC 2A conclusion—"probably carcinogen to humans"--essentially means. But one of the seminal tenets of toxicology is that "the dose makes the poison," and the reality is that glyphosate is not a human health risk even at levels of exposure that are more than 100 times higher than the human exposures that occur under conditions consistent with the product's labeling.

Thus, IARC publishes qualitative assessments that are not quantitative assessments of risk. That is left to regulatory agencies. So, what have they concluded? Glyphosate is currently undergoing a routine review of its registration in Europe, which is being conducted by the German Risk Agency (BfR). This re-registration evaluation has been going on since 20XX and as of January 2015 the BfR [HYPERLINK "http://www.bfr.bund.de/en/the_bfr_has_finalised_its_draft_report_for_the_re_evaluation_of_glyphosate-188632.html"]:

- In conclusion of this re-evaluation process of the active substance glyphosate by BfR the available data do not show carcinogenic or mutagenic properties of glyphosate nor that glyphosate is toxic to fertility, reproduction or embryonal/fetal development in laboratory animals.

- In epidemiological studies in humans, there was no evidence of carcinogenicity and there were no effects on fertility, reproduction and development of neurotoxicity that might be attributed to glyphosate."

Regulatory agencies typically review more data and in much more depth than the IARC. For glyphosate, there have been X companies (name them) that submitted data from multiple types of studies which are evaluated by the U.S. EPA, the German BfR and other global regulatory agencies. They also take into consideration studies like the United States' Agricultural Health Study (AHS), a prospective study of cancer in licensed pesticide applicators and their spouses from Iowa and North Carolina. The study is a collaborative effort involving investigators from National Cancer Institute, the National Institute of Environmental Health Sciences, the EPA, and the National Institute for Occupational Safety and Health. By studying high-exposure individuals such as pesticide applicators, carcinogens can be identified.

The bottom line is that the BfR examined all of the information that IARC saw and much more.

New data are emerging constantly, and there have been new scientific reviews published recently that would have been unavailable to BfR before they issued their sanguine opinion. So, could any of these new documents have led IARC to their less favorable conclusion? Nope, because these reviews further affirmed the safety of glyphosate and the absence of no linkage between glyphosate and cancer risk.

Consider the conclusion of [HYPERLINK "http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423"] in the March 2105 issue of Critical Reviews in Toxicology:

> "The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans."

And this, from an [HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/25635915"] in the International Journal of Environmental Research and Public Health in January 2015:

> "There were no statistically significant trends for multiple myeloma risks in relation to reported cumulative days (or intensity weighted days) of glyphosate use. The doubling of risk reported previously arose from the use of an unrepresentative restricted dataset and analyses of the full dataset provides no convincing evidence in the AHS for a link between multiple myeloma risk and glyphosate use."

What does IRAC's decision mean to consumers and farmers? Nothing. They should feel confident that global regulatory agencies will continue to do their risk assessments with the proper amount of scientific rigor and to make the critical distinction between hazard and risk.

In June, the IARC will evaluate three more pesticides. My bet is that none of them will get through unscathed. That's a much surer thing that my predictions about March Madness.

Henry I. Miller, a physician and molecular biologist, is the Robert Wesson Fellow in Scientific Philosophy and Public Policy at Stanford University's Hoover Institution. He was the founding director of the FDA's Office of Biotechnology.