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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

v.

MONSANTO COMPANY

Defendants.

Case No. CGC-16-550128

REQUEST FOR JUDICIAL NOTICE IN SUPPORT OF PLAINTIFF'S REPLY BRIEF IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT

Trial Date: June 18, 2018
Time: 9:30 a.m.
Department: TBD

TO EACH PARTY AND THEIR ATTORNEYS OF RECORD:

YOU ARE HEREBY NOTIFIED THAT, pursuant to California Evidence Code sections 451, 452 and 453, and California Code of Civil Procedure section 437c(b), Plaintiff will and hereby does request that this Court take judicial notice of the following public records and documents in connection with Plaintiff's Reply Brief in Support of Plaintiff's Motion for Partial Summary Judgment.

1. Attached hereto as Exhibit 1 is a true and correct copy of the web page, "About the NPIC", NPIC website, http://npic.orst.edu/about.html

2. Attached hereto as Exhibit 2 is a true and correct copy of the web page, Information on Health Risks of Pesticides, EPA website, https://www.epa.gov/safepestcontrol/pesticides-must-be-registered-epa

3. Attached hereto as Exhibit 3 is a true and correct copy of the Glyphosate General Fact Sheet, NPIC website, http://npic.orst.edu/factsheets/glyphogen.html .

4. Attached hereto as Exhibit 4 is a true and correct copy of the, EPA Label Review Manual, Chapter 15: Company Name and Address, 15-3.

5. Attached hereto as Exhibit 5 is a true and correct copy of Robert, et al., EPA, "Recognition And Management Of Pesticide Poisonings", Sixth Edition, 2013, p. 2.

6. Attached hereto as Exhibit 6 is a true and correct copy of a July 1, 1983 EPA memorandum and report detailing its findings regarding the fraud at Industrial Biotest Laboratories.

7. Attached hereto as Exhibit 7 is a true and correct copy of a September 4, 1984, EPA memorandum and report detailing its finding that glyphosate is a possible oncogene.

8. Attached hereto as Exhibit 8 is a true and correct copy of a March 4, 1985 EPA memorandum and report detailing its finding that glyphosate is a possible oncogene.

9. Attached hereto as Exhibit 9 is a true and correct copy of a June 14, 1985 EPA memorandum and report detailing its finding that Monsanto's statistical arguments are not valid.

10. Attached hereto as Exhibit 10 is a true and correct copy of a February 26, 1985 EPA memorandum and report detailing its findings that Monsanto's argument regarding the oncogenicity of glyphosate are not valid.

11. Attached hereto as Exhibit 11 is a true and correct copy of a December 4, 1985 EPA memorandum and report detailing a pathological finding by and EPA pathologist.

12. Attached hereto as Exhibit 12 is a true and correct copy of a January 15, 1988 EPA memorandum requesting Monsanto to conduct a repeat Mouse study.

13. Attached hereto as Exhibit 13 is a true and correct copy of a May 3, 2016 email from Jim Jones to EPA Administrator McCarthy stating that the OPP review of glyphosate did not follow EPA guidelines.

14. Attached hereto as Exhibit 14 is a true and correct copy of the March 16, 2017, FIFRA Scientific Advisory Panel Meeting Minutes and Final Report.

15. Attached hereto as Exhibit 15 is a true and correct copy of the EPA's Office of Research and Development's "Summary of ORD's Comments on OPP glyphosate issue paper"

16. Attached hereto as Exhibit 16 is an email to Jess Rowland from Michael Goodis of the EPA regarding coordinating with EFSA to disagree with IARC prior to the release of IARC's evaluation of glyphosate.

17. Attached hereto as Exhibit 17 is an email from Vince Cogliano of the EPA to Norman Birchfield of the EPA noting the EPA's Office of Research and Development's disagreement with the OPP glyphosate issue paper.

18. Attached hereto as Exhibit 18 is the July 7, 2017 notice by the State of California Adding glyphosate to a list of chemicals known to cause cancer under Proposition 65.

19. Attached hereto as Exhibit 19 is the California Office of Environmental Health Hazard Assessment's April 19, 2018 final statement of Reasons for the Establishment of the NSRL for glyphosate.

Legal Authority:

California Evidence Code Sections 452 (c), (d), (g), and (h) state, in pertinent part:

Judicial notice may be taken of the following matters to the extent that they are not embraced within Section 451:

> (c) Official acts of the legislative, executive, and judicial departments of the United States and of any state of the United States.

(d) Records of (1) any court of this state or (2) any court of record of the United States or of any state of the United States

(g) Facts and propositions that are of such common knowledge within the territorial jurisdiction of the court that they cannot reasonably be the subject of dispute.

(h) Facts and propositions that are not reasonably subject to dispute and are capable of immediate and accurate determination by resort to sources of reasonably indisputable accuracy.

Evid. Code. § 452 (c), (d), (g), and (h).

Courts may take judicial notice of "official acts of the legislative, executive, and judicial departments of the United States and of any state of the United States." *Rodas v. Spiegel*, 87 Cal. App. 4th 513, 518 (Cal. App. 2d Dist. 2001) [citing Evid. Code, § 452, subd. (c)]. Official acts include records, reports and orders of administrative agencies. Id. [citing (*Hogen v. Valley Hospital*, 147 Cal. App. 3d 119, 125 (Cal. App. 2d Dist. 1983); *McGlothlen v. Department of Motor Vehicles*, 71 Cal. App. 3d 1005, 1015 (Cal. App. 1st Dist. 1977); *Agostini v. Strycula*, 231 Cal. App. 2d 804, 806 (Cal. App. 1st Dist. 1965)]. Manuals and publications are among the records that may be judicially noticed. *In re H.C.*17 Cal.App.5th 1261, 1268, 226 Cal.Rptr.3d 424, 428 ("We may take judicial notice of this portion of the Child Welfare Policy Manual because its publication is an official act of an executive department of the federal government.").

Furthermore:

The trial court shall take judicial notice of any matter specified in Section 452 if a party requests it and:
(a) Gives each adverse party sufficient notice of the request, through the pleadings or otherwise, to enable such adverse party to prepare to meet the request; and
(b) Furnishes the court with sufficient information to enable it to take judicial notice of the matter.

Cal. Evid. Code § 453 (West).

Here, Defendants were informed via email that Plaintiff's would seek judicial notice of these documents on May 31, 2018. This filed notice and request will provide Defendant sufficient opportunity to respond prior to the use of these documents at trial. The documents are attached to this Request thereby furnishing the court with sufficient information to enable it to take judicial notice.

Exhibits 1-5:

Exhibits 1 and 3 are official publications of the National Pesticide Information Center, which is a collaboration between the EPA and the state of Oregon and are posted on Oregon State University's website intended to provide information about the risks of pesticides. Exhibit 3 is a glyphosate fact sheet created by this collaboration between the EPA and Oregon State University on glyphosate meant to inform the public about the risks of glyphosate. *See Salleng v. Oregon State Univ.*, No. CIV. 10-06073-HO, 2010 WL 3199953, at *2 (D. Or. Aug. 10, 2010), aff'd, 456 F. App'x 706 (9th Cir. 2011) (Oregon State University is a government agency.) Exhibit 2 is a report from the EPA describing its funding of the NPIC and the purpose of the NPIC. Exhibits 4 and 5 are official manuals and guidelines created by or in conjunction with the EPA and posted on the EPA website. These documents all constitute official acts of federal and state governments under Evid. Code. § 452 (c) and are easily verifiable under § 452 (h).

These documents are relevant to trial in this case because one defense by Monsanto is that because the EPA has approved a glyphosate label without a warning for NHL, they are therefore prohibited from warning consumers about the risk of NHL.

The Office of Pesticide Programs, ("OPP") would allow and currently allows warnings about the risk of NHL with glyphosate to be issued to the public. The organization charged by the EPA in responding to inquiries about the risks of pesticides is the National Pesticide Information Center ("NPIC"). The "NPIC is a cooperative agreement between Oregon State University and the U.S. Environmental Protection Agency" that "provides objective, science-based information about pesticides and pesticide-related topics to enable people to make informed decisions about pesticides and their use." Exhibit 1. The EPA website directs users to the NPIC to find out about the risks of pesticides. Exhibit 2. Currently, the NPIC advises consumers the following in a fact sheet available on its website:

> Is glyphosate likely to contribute to the development of cancer?
>
> When high doses were administered to laboratory animals, some studies suggest that glyphosate has carcinogenic potential. Studies on cancer rates in people have provided conflicting results on whether the use of glyphosate containing products is associated with cancer. **Some studies have associated glyphosate use with non-Hodgkin lymphoma**.

Exhibit 3. In its guidance to pesticide manufacturers, the EPA actually allows the manufacturers to direct consumers to the NPIC to obtain information about the health effects of glyphosate:

> The Agency strongly encourages that labels include a company telephone number or a toll-free hotline number that allows users to obtain additional product information. PR Notice 97-4. This is intended for non-emergency product information and is different from the emergency treatment information number (e.g. poison control) that is listed under the First Aid section. **As an option, the National Pesticide Information Center (NPIC) hotline number may be used**, with the suggested statement: "For information on this pesticide product (including general health concerns or pesticide incidents), call the National Pesticide Information Center at 1-800-858-7378, Monday through Friday, 8:00 AM to 12:00 PM Pacific Standard Time. In the event of a medical emergency, call your poison control center at 1-800-222-1222."

Exhibit 4. Therefore, not only could Monsanto inform the public that glyphosate is associated with NHL via the NPIC, the EPA encourages them to do just that.

Additionally, in a collaboration between the EPA and the Medical University of South Carolina, physicians are also warned of the association between glyphosate and NHL. This publication by the EPA, "Recognition and Management of Pesticide Poisonings" was created "to provide healthcare professionals with current consensus recommendations for treating patients with pesticide-related illnesses or injuries." Exhibit 5, p. 2. In the chapter on chronic diseases, the EPA identifies glyphosate as one of the pesticides that has a "demonstrated risk" of NHL. Exhibit 5 at 222.

These documents are also all relevant to causation because it shows that independent scientists at the EPA agree with Plaintiff that glyphosate based herbicides can increase the risk of NHL.

Exhibit 6:

Exhibit 6 is an official final report by the EPA, published in 1983, detailing its findings on the Industrial Biotest Laboratories scandal. This document is available through the EPA's website. The report details rampant fraud at the laboratory, and demonstrates the most of the studies supporting the approval of sale of glyphosate were performed at this laboratory and the results were invalid. This document constitutes an official act of the federal government under Evid. Code. § 452 (c) and it is easily verifiable under § 452 (h). The admissibility of this document is the subject of Monsanto's Motion in Limine No. 6, and the arguments have been fully briefed by both sides.

Exhibits 7-12:

These documents are all official reports of EPA scientists who analyzed a 1983 mouse carcinogenicity study submitted by Monsanto and concluded that the glyphosate was a possible human

carcinogen based on these studies. These scientists further requested that Monsanto repeat the mouse test and Monsanto refused. These documents are all available on the EPA's website. These documents all constitute official acts of federal and state governments under Evid. Code. § 452 (c) and are easily verifiable under § 452 (h). The admissibility of these documents is the subject of Monsanto's Motion in Limine No. 24 and the arguments have been fully briefed by both sides

Exhibits 13-15, 17:

These documents are all official reports and records of EPA scientists who disagree with the EPA's Office of Pesticide Programs draft conclusion that glyphosate is unlikely to be carcinogenic. Exhibit 13 is an email, released via a FOIA request, from Jim Jones an assistant administrator at the EPA to then Administrator Gina McCarthy stating that the scientists at the OPP failed to follow established EPA guidelines in evaluating glyphosate. Exhibit 14 is the Final Report and Meeting Minutes of the December 2016, Scientific Advisory Panel ("SAP") which convened to evaluate the OPP's draft assessment of glyphosate. Hoke Decl., Ex. 42. The SAP "serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP)". Id. at p. 3. The Panel unanimously concluded that "the EPA evaluation does not appear to follow the EPA (2005) Cancer Guidelines." Id. at p. 18. Some of the members found that "there are sufficient data to conclude glyphosate is a rodent carcinogen using the approaches recommended to interpret the biological significance of tumor responses in EPA's 2005 Guidelines for Carcinogen Risk Assessment." Id.

The Office of Research and Development Branch of the EPA also reviewed the evidence related to glyphosate and concluded in Exhibit 17 that "Bottom line: Based on glyphosate discussions to date among ORD scientists – where we have not formally discussed a classification – I believe we would be split between 'likely to be carcinogenic' and 'suggestive evidence.'" Exhibit 17 is an email released via a FOIA request to the EPA. The report issued by the ORD, exhibit 15, concludes also that "[t]he OPP draft risk assessment does not appear to follow" the approaches listed in the EPA guidelines. The ORD further noted their agreement with IARC on the epidemiology. These documents all constitute official acts of federal and state governments under Evid. Code. § 452 (c) and are easily verifiable under § 452 (h). Exhibit 15 was also released via a FOIA request to the EPA.

These documents are relevant to trial because Monsanto will use as a defense the fact that the OPP has issued a draft assessment concluding that glyphosate is not likely to be carcinogenic.

Monsanto will suggest that the EPA is a monolithic organization which made a collective decision. That is not true. These documents demonstrate that many scientists at the EPA disagreed with the OPP's draft conclusion. These documents also demonstrate that there is a consensus that the OPP did not follow its own guidelines in evaluating glyphosate. The OPP's failure to follow guidelines makes its conclusion about glyphosate less credible.

Exhibit 16:

Exhibit 16 is an email between two OPP employees, Jess Rowland, head of the Cancer Assessment Review Committee in charge of evaluating glyphosate and Michael Goodis. This email was released via a FOIA request to the EPA. This email discusses coordination between the European Food Safety Agency and the EPA in evaluating glyphosate. The email occurred in May 2015, two months before IARC released its detailed assessment of glyphosate and the reasoning behind its finding that glyphosate was probably carcinogenic. The email also occurred before the OPP and EFSA's evaluation of the carcinogenicity of glyphosate. Despite not conducting any evaluation, the email demonstrates that both EFSA and EPA were going to conclude, *a priori,* that glyphosate was not carcinogenic. Michael Goodis tells Jess Rowland, "I was approached by EFSA about glyphosate. They are planning to issue a review including a cancer classification in Aug. They are saying they will disagree with IARC and will be more in line with us, and would like a point of contact within OPP as it leads up to that." This document constitutes an official act of the federal government under Evid. Code. § 452 (c) and it is easily verifiable under § 452 (h).

This document is relevant to trial because Monsanto intends to use as a defense the fact that the EPA and several other foreign regulatory bodies have disagreed with IARC. This document demonstrates that the OPP and EFSA were coordinating their efforts and were not impartial in their evaluation of glyphosate. Both agencies concluded that glyphosate was not carcinogenic before evaluating the data, which make their evaluations of glyphosate less credible. Independent scientists review the data before developing a conclusion.

Exhibit 18, 19:

Exhibit 18 is California Office of Environmental Health Hazard Assessment's ("OEHHA") formal notice that it is listing glyphosate as a chemical known to cause cancer pursuant to Proposition 65. Exhibit 19 is OEHHA's final statement of reasons for establishing a No Significant Risk Level for determining how much glyphosate exposure is necessary to cause cancer, wherein OEHHA notes

its agreement with IARC that glyphosate is carcinogenic and genotoxic. Proposition 65 listings are properly subject to judicial notice. *Cooper v. Takeda Pharm. Am., Inc.,* 239 Cal. App. 4th 555, 565, 191 Cal. Rptr. 3d 67, 74 (2015) ("We granted Cooper's request to take judicial notice of the fact that in April 2014, the Office of Environmental Health Hazard Assessment added pioglitazone to the list of chemicals known to the State of California to cause cancer for the purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).") The admissibility of these documents is the subject of Monsanto's Motion in Limine No. 27 and the arguments have been fully briefed by both sides.

CONCLUSION:

For the Aforementioned reasons Plaintiff respectfully requests that the Court take judicial notice of the above-referenced documents.

DATED: June 18, 2018

Respectfully submitted,

THE MILLER FIRM, LLC

By: */s/ Curtis G. Hoke*

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EXHIBIT 1

npic NATIONAL PESTICIDE INFORMATION CENTER

About NPIC

NPIC provides objective, science-based information about pesticides and pesticide-related topics to enable people to make informed decisions about pesticides and their use. NPIC is a cooperative agreement between Oregon State University and the U.S. Environmental Protection Agency.

The objectives of NPIC are:

1. To serve as a factual source of information for diverse professional and public audiences on pesticide-related issues;
2. To operate a toll-free, bi-lingual telephone information service for all callers in the United States and its territories, Monday through Friday at least 4 hours per day, with accessibility to voicemail during closed hours, and ability to address inquiries through e-mail and social media;
3. To develop and maintain English and Spanish websites accessible to broad audiences and host NPIC original content, state-of-the-art information technology tools and links to unbiased and authoritative sources of information about pesticides;
4. To collect robust pesticide incident data through systematic protocols and to disseminate the information through scheduled reporting and by request from U.S. EPA and partner agencies;
5. To conduct our service professionally, with an emphasis on teamwork, integrity and accountability, and a strong commitment to collaboration and exceptional customer service.

Click on the headphone icon to the left to download and listen to a short **PestiByte PODcast** describing NPIC services. Look for the PestiByte headphone icon on other pages, including **Common Pesticide Questions** page for **more PODcast downloads!**

Foreign Language Capability:

NPIC can assist people in over 240 different **languages** through the use of an over-the-phone language service with staff trained in medical and scientific terminology. This same service is used by numerous poison control centers across the United States.

NPIC Publications:

NPIC produces many types of **publications** including research papers, **frequently asked questions**, **annual reports**, **outreach materials**, **podcasts** and other resources available to the public. Click **here** to see a complete list of publications.

Related Topics:

- NPIC Publications
- NPIC Disclaimers

What are pests?

- Learn about a pest
- Identify a pest
- Control a pest
- Integrated Pest Management

What are pesticides?

- Herbicides
- Disinfectants
- Fungicides
- Insecticides
- Natural and Biological Pesticides
- Repellents
- Rodenticides
- Other types of pesticides

Disponible en español

About the NPIC Web Site

All the pages in this site contain valid **HTML 4.01 Strict** and valid **CSS**

All the pages in this site conform to W3C's "Web Content Accessibility Guidelines 1.0", level Double-A.

If you have questions about this, or any pesticide-related topic, please call NPIC at **1-800-858-7378** (8:00am - 12:00pm PST), or email us at **npic@ace.orst.edu**.

Last updated March 20, 2017

NPIC provides objective, science-based information about pesticides and pesticide-related topics to enable people to make informed decisions. NPIC is a cooperative agreement between **Oregon State University** and the **U.S. Environmental Protection Agency** (cooperative agreement #X8-83560101). The information in this publication does not in any way replace or supersede the restrictions, precautions, directions, or other information on the pesticide label or any other regulatory requirements, nor does it necessarily reflect the position of the U.S. EPA.

EXHIBIT 2

United States Environmental Protection Agency

Pesticides Must be Registered with EPA

Pesticides must be registered with EPA unless they meet the criteria for a minimum risk pesticide. EPA evaluates pesticides to ensure that when they are used according to label directions they will not harm people, non-target species or the environment. Our evaluation includes assuring that using the pesticide according to label directions does not pose risks to vulnerable populations, including children and pregnant women.

EPA examines:

- the ingredients of a pesticide;
- where it will be used (e.g., in the home or on food);
- the amount, frequency and timing of its use; and
- how it will be discarded or stored. Read about:
  - Safe storage of pesticides.
  - How to dispose of pesticides.

Companies are required to submit to EPA for review information about the health effects of pesticides, including:

- cancer,
- reproductive effects,
- neurological effects, and
- acute and chronic toxic effects.

EPA also funds pesticide research engaging the nation's best scientists and engineers to improve knowledge about how we are exposed to pesticides and their health effects.

Once registered, pesticides are periodically reviewed for safety. If new concerns arise, EPA can change the conditions for using them or cancel their registrations.

It is illegal to use a pesticide product inconsistent with its label directions.

In addition, there are a variety of illegal, unregistered pesticide products in the marketplace that can pose risks to you and your family. Learn more about the risks of these products and how to avoid them.

Tips for reducing pesticide impacts on wildlife.

Information on Health Risks of Pesticides

EPA has a cooperative agreement with Oregon State University, which operates The National Pesticide Information Center (NPIC). This center provides objective, science-based information about a variety of pesticide-related subjects, including pesticide products, recognition and management of pesticide poisonings, toxicology, and environmental chemistry. NPIC also lists state pesticide regulatory agencies, and provides links to their Web sites NPIC can be contacted at: 1-800-858-7378 or by email at npic@ace.orst.edu.

For more information, visit the NPIC website. EXIT

LAST UPDATED ON JUNE 19, 2017

EXHIBIT 3

Glyphosate

General Fact Sheet

What is glyphosate?

Related Topics:

Glyphosate Overview

PDF Version

What are pests?

Learn about a pest

Identify a pest

Control a pest

Integrated Pest Management

What are pesticides?

Herbicides

Disinfectants

Fungicides

Insecticides

Natural and Biological Pesticides

Repellents

Rodenticides

Other types of pesticides

Glyphosate is an herbicide. It is applied to the leaves of plants to kill both broadleaf plants and grasses. The sodium salt form of glyphosate is used to regulate plant growth and ripen fruit.

Glyphosate was first registered for use in the U.S. in 1974. Glyphosate is one of the most widely used herbicides in the United States. People apply it in agriculture and forestry, on lawns and gardens, and for weeds in industrial areas. Some products containing glyphosate control aquatic plants.

What are some products that contain glyphosate?

Glyphosate comes in many forms, including an acid and several salts. These can be either solids or an amber-colored liquid. There are over 750 products containing glyphosate for sale in the United States.

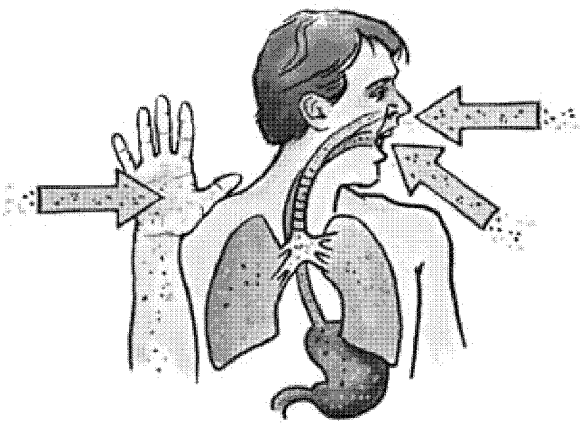
Always follow label instructions and take steps to avoid exposure. If any exposures occur, be sure to follow the First Aid instructions on the product label carefully. For additional treatment advice, contact the Poison Control Center at 1-800-222-1222. If you wish to discuss a pesticide problem, please call 1-800-858-7378.

How does glyphosate work?

Glyphosate is a non-selective herbicide, meaning it will kill most plants. It prevents the plants from making certain proteins that are needed for plant growth. Glyphosate stops a specific enzyme pathway, the shikimic acid pathway. The shikimic acid pathway is necessary for plants and some microorganisms.

How might I be exposed to glyphosate?

You can be exposed to glyphosate if you get it on your skin, in your eyes or breathe it in when you are using it. You might swallow some glyphosate if you eat or smoke after applying it without washing your hands first. You may also be exposed if you touch plants that are still wet with spray. Glyphosate isn't likely to vaporize after it is sprayed.

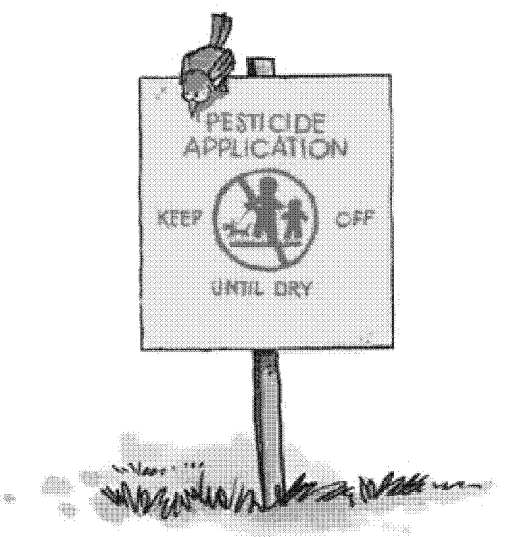


What are some signs and symptoms from a brief exposure to glyphosate?

Pure glyphosate is low in toxicity, but products usually contain other ingredients that help the glyphosate get into the plants. The other ingredients in the product can make the product more toxic. Products containing glyphosate may cause eye or skin irritation. People who breathed in spray mist from products containing glyphosate felt irritation in their nose and throat. Swallowing products with glyphosate can cause increased saliva, burns in the mouth and throat, nausea, vomiting, and diarrhea. Fatalities have been reported in cases of intentional ingestion.

Pets may be at risk if they touch or eat plants that are still wet with spray from products containing glyphosate. Animals exposed to products with glyphosate may drool, vomit, have diarrhea, lose their appetite, or seem sleepy.

What happens to glyphosate when it enters the body?



In humans, glyphosate does not easily pass through the skin. Glyphosate that is absorbed or ingested will pass through the body relatively quickly. The vast majority of glyphosate leaves the body in urine and feces without being changed into another chemical.

Is glyphosate likely to contribute to the development of cancer?

When high doses were administered to laboratory animals, some studies suggest that glyphosate has carcinogenic potential. Studies on cancer rates in people have provided conflicting results on whether the use of glyphosate containing products is associated with cancer. Some studies have associated glyphosate use with non-Hodgkin lymphoma.

Has anyone studied non-cancer effects from long-term exposure to glyphosate?

Glyphosate exposure has been linked to developmental and reproductive effects at high doses that were administered to rats repeatedly during pregnancy. These doses made the mother rats sick. The rat fetuses gained weight more slowly, and some fetuses had skeletal defects. These effects were not observed at lower doses.

No information was found linking exposure to glyphosate with asthma or other diseases.

Are children more sensitive to glyphosate than adults?

While **children may be especially sensitive to pesticides** compared to adults, there are currently no data showing that children have increased sensitivity specifically to glyphosate.

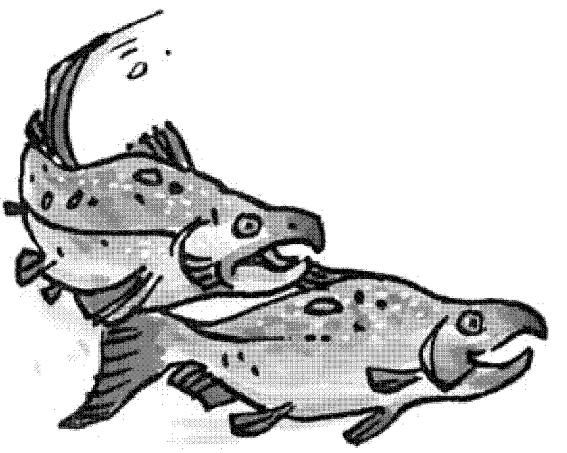
What happens to glyphosate in the environment?

Glyphosate binds tightly to soil. It can persist in soil for up to 6 months depending on the climate and the type of soil it is in. Glyphosate is broken down by bacteria in the soil.

Glyphosate is not likely to get into groundwater because it binds tightly to soil. In one study, **half** the glyphosate in dead leaves broke down in 8 or 9 days. Another study found that some glyphosate was taken up by carrots and lettuce after the soil was treated with it.

Can glyphosate affect birds, fish, or other wildlife?

Pure glyphosate is low in toxicity to fish and wildlife, but some products containing glyphosate may be toxic because of the other ingredients in them. Glyphosate may affect fish and wildlife indirectly because killing the plants alters the animals' habitat.



Where can I get more information?

For more detailed information about glyphosate please visit the list of **referenced resources** or call the National Pesticide Information Center, Monday - Friday, between 8:00am - 12:00pm Pacific Time (11:00am - 3:00pm Eastern Time) at 1-800-858-7378 or visit us on the web at **http://npic.orst.edu**. NPIC provides objective, science-based answers to questions about pesticides.

Please cite as: Henderson, A. M.; Gervais, J. A.; Luukinen, B.; Buhl, K.; Stone, D. 2010. ***Glyphosate General Fact Sheet***; National Pesticide Information Center, Oregon State University Extension Services. http://npic.orst.edu/factsheets/glyphogen.html.

Date Reviewed: 2015

NPIC fact sheets are designed to answer questions that are commonly asked by the general public about pesticides that are regulated by the U.S. Environmental Protection Agency (U.S. EPA). This document is intended to be educational in nature and helpful to consumers for making decisions about pesticide use.

EXHIBIT 4

Revised August 2017

Label Review Manual

Chapter 15: Company Name and Address

http://commons.wikimedia.org, photo by "Daderot"

Note that:

- If more than one company is given, appropriate qualifiers should be used.
- The company name cannot be abbreviated unless it is easily-recognizable as an abbreviation of its full name.
- If the company name is "a division of", "a subsidiary of", "c/o" (care of), or "dba" (d/b/a or doing business as) another company, the name(s) given on the label should match the Agency's records.
- The company address should include the street address and/or PO Box™, plus ZIP Code™ of the location where correspondence may be sent.
- An authorized, designated agent's name and address may be used instead of or in addition to the company's name and address.
- For foreign registrants, the United States address of record may be used instead of or in addition to the foreign address.

V. Non-emergency telephone number

The Agency strongly encourages that labels include a company telephone number or a toll-free hotline number that allows users to obtain additional product information. PR Notice 97-4. This is intended for non-emergency product information and is different from the emergency treatment information number (e.g. poison control) that is listed under the First Aid section.

As an option, the National Pesticide Information Center (NPIC) hotline number may be used, with the suggested statement:

> "For information on this pesticide product (including general health concerns or pesticide incidents), call the National Pesticide Information Center at 1-800-858-7378, Monday through Friday, 8:00 AM to 12:00 PM Pacific Standard Time. In the event of a medical emergency, call your poison control center at 1-800-222-1222."

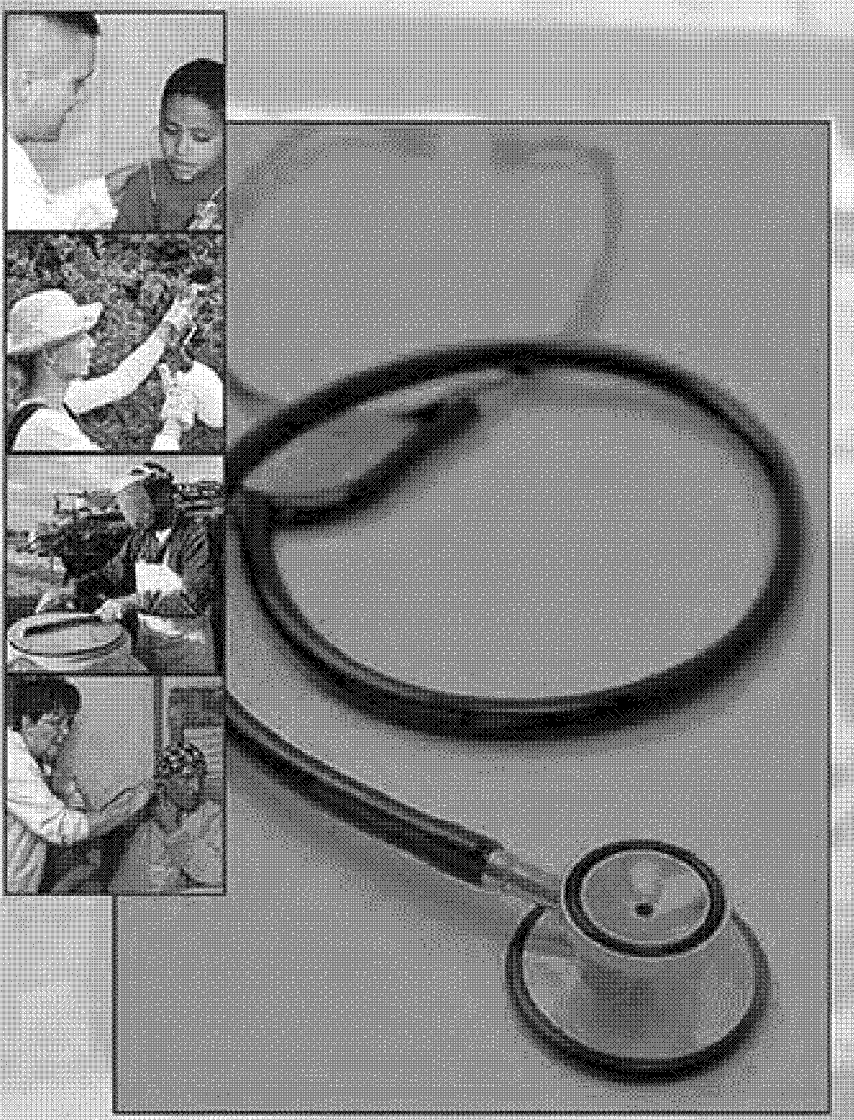
Note that the NPIC, formerly called the National Pesticide Telecommunications Network (NPTN), has decreased their hours of operation from 6:30 AM to 4:30 PM PST seven days a week to 8:00 AM to 12:00 PM PST Monday through Friday. However, NPIC staff will typically respond to all inquiries received through voice mail, email, or social media within one business day.

EXHIBIT 5

United States Environmental
Protection Agency
Office of Pesticide Programs

EPA 735K13001

Recognition and Management of Pesticide Poisonings



Sixth Edition

RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

Sixth Edition • 2013

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This edition was peer reviewed by experts in clinical toxicology. We greatly appreciate the efforts of the following reviewers:

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Bottom color photo on the cover (clinician and worker) © earldotter.com, courtesy Migrant Clinicians Network.

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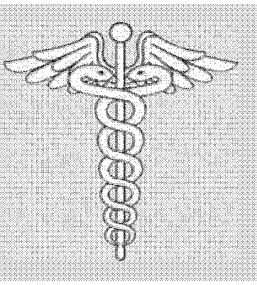
GENERAL INFORMATION

CHAPTER 1

Introduction

The purpose of this manual is to provide healthcare professionals with current consensus recommendations for treating patients with pesticide-related illnesses or injuries. The Office of Pesticide Programs of the U.S. Environmental Protection Agency has sponsored the series since 1973. The 5th edition of this manual was published in 1999; since then, much has changed with regard to the pesticide products on the market. Most indoor uses of organophosphates have been eliminated, and a combination of EPA risk mitigation actions has limited their use on food crops. Pyrethroids have largely replaced organophosphates for residential pest control. While this conversion is beneficial in that the risk to human health is lower with this relatively less acutely toxic class of pesticide, it introduces a new set of health issues for consideration. Many new pesticide products have been registered and are not necessarily widely known among health professionals. This 6th edition includes a chapter that explores potential association between low-level exposure to pesticides over time and chronic diseases.



Treatments for pesticide exposure carry health risks of their own.

There is general agreement that *prevention* of pesticide poisoning remains a much surer path to safety and health than reliance on treatment. In addition to the inherent toxicity of pesticides, none of the medical procedures or drugs used in treating poisonings is risk free. In fact, many antidotes are toxic in their own right, and such apparently simple procedures as gastric intubation involve substantial risk. The clinician must weigh the hazards of various courses of action (including no treatment at all) against the risks of various interventions, such as gastric emptying, catharsis, administration of intravenous fluids or administration of an antidote, if available. Clinical management decisions have to be made promptly and, as often as not, on the basis of limited scientific and medical information. The complex circumstances of human poisonings rarely allow for precise comparisons of alternative management strategies. Therefore, it is important for the reader to keep in mind that the treatment recommendations in this book do not guarantee successful outcomes. They are merely consensus judgments of the best available clinical management options. Clinical toxicology is a dynamic field of medicine; new treatment methods are developed regularly, and the effectiveness of old as well as new modalities is subject to constant critical review.

Associations between Pesticides and Cancer in Adults

Bassil et al. conducted a systematic review of cancer and pesticides, which included studies of children and of adults. Each study was evaluated for methodological quality by two trained reviewers using a standardized assessment tool with a high inter-rater reliability. Only studies with a global rating of 4 or higher were included in the review.[2]

Many of the studies evaluating relationships between cancers in adults and pesticides are conducted in the occupational setting. Associations between pesticide exposure and the development of leukemia and non-Hodgkin lymphoma were noted in most studies. Solid tumors of the prostate, pancreas, kidney and breast were among the more consistently reported findings in studies of adults. As was noted in numerous studies of childhood outcomes, ascertainment of whether exposure actually occurred and the amount of exposure are recurring weaknesses in adult studies.

*Tumors of the prostate, pancreas, kidney and breast have been among the more consistently **reported findings.***

Non-Hodgkin Lymphoma and Other Hematopoietic Cancers

Of the 27 studies on non-Hodgkin lymphoma (NHL) that met quality criteria in the Bassil review, 23 found positive associations. Almost half of these studies were conducted in adult cohorts of various occupational groups including farmers, pesticide applicators, landscapers and those who worked in pesticide manufacturing. Ten of the 12 cohort studies reported a positive association, with four reaching statistical significance. One of the larger cohort studies demonstrated a relative risk RR of 2.1, 95% CI, 1.1-3.9. Eleven of the 13 case-control studies (excludes one positive study in children) also demonstrated an association between occupational exposure and NHL, with 7 reaching statistical significance. Multiple classes of pesticides were implicated.[2]

A separate meta-analysis of case-control studies examining the relationship between pesticide exposure and hematopoietic cancers was published in 2007. The authors reviewed 36 case-control studies. After excluding studies with methodological flaws or data concerns, a study that included non-hematopoietic cancers and a study written in Italian, 13 studies remained for analysis. The cancers assessed in the meta-analysis were NHL, leukemia and multiple myeloma.[72] The overall meta-OR for NHL was 1.35, 95% CI, 1.2-1.5. An increased risk for leukemia and multiple myeloma was also demonstrated, though both were just short of reaching statistical significance (OR = 1.35, 95% CI, 0.9-1.2 and OR = 1.16, 95% CI, 0.99-1.36). The authors also conducted a meta-regression to account for the heterogeneity among the studies. They found that exposure for longer than 10 years increased the risk for all hematopoietic cancers (mOR = 2.18, 95% CI, 1.43-3.35) and for NHL (mOR = 1.65, 95% CI, 1.08-2.51).[72]

As with other cancer epidemiologic studies discussed above, the major limitation was the lack of sufficient exposure information in many of the studies. Additionally, the cohort studies in the above meta-analysis only listed the class of pesticide and the corresponding OR (herbicides or insecticides) rather than the individual pesticide.[72] Other individual studies have demonstrated risks from certain specific pesticides. One well-designed cohort study reported risks associated with mecoprop, a chlorophenoxy herbicide.[73] Another study demonstrated risks from another chlorophenoxy herbicide methyl phenoxyacetic acid (MCPA) and from glyphosate.[74] Another study demonstrated a significant increased risk of NHL for subjects exposed to 2,4-D.[75] The Agricultural Health Study demonstrated a risk of developing leukemia following exposure to diazinon.[76]

Prostate Cancer

It has been suspected that pesticide exposure may be associated with prostate cancer. This association may be related to hormonally active pesticides, known as endocrine

EXHIBIT 6

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUMMARY OF THE IBT REVIEW PROGRAM

OFFICE OF PESTICIDE PROGRAMS

JULY 1983

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

The IBT Review Program

This report summarizes the findings of the joint program conducted by the Environmental Protection Agency (EPA) and the Health Protection Branch of Health and Welfare Canada to reexamine the validity of health effects studies on pesticides tested by Industrial Bio-Test Laboratories, Inc. (IBT). This program is one result of discoveries made during a series of audits beginning in 1976 by the Food and Drug Administration (FDA) and EPA which revealed serious deficiencies in IBT tests conducted to support the registration of numerous pesticides and some drugs in both the United States and Canada. This report assesses the impact of the IBT situation on the registration status of the chemicals involved and describes the steps the Agency has taken to resolve this problem and to prevent its recurrence.

Exhibit A shows how many IBT and non-IBT tests are available to EPA in each testing category for the pesticide chemicals having some IBT conducted studies in their data base. As these tables show, a large majority (93%) of the pesticides tested by IBT, also have non-IBT data available. Only 12 of the pesticides listed have a data base entirely of IBT studies. However, seven of these are either not registered for use in this country or are cancelled or discontinued products. Some of the IBT studies on the remaining five chemicals are at least partially valid or "supplemental", meaning the data can be used to support the findings of other studies.

These tables also indicate the pesticides for which new data have been required as a result of EPA regulatory actions. These include risk/benefit reviews undertaken because of specific evidence of a hazard (known as Rebuttable Presumption Against Registration, listed as "RPAR" in tables) or EPA's regular program for reregistering all previously registered pesticides (in tables, "Registration Standard" and "Data Call-In"). The reregistration program is not specifically connected to the IBT case, but serves the purpose of bringing the data on older chemicals, including some tested by IBT, up to current scientific standards. Under the authority of section 3(c)(2)(B) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) the Agency can require additional data to maintain a registration, and may suspend a product's registration if the registrant does not agree to provide the data or if it is not provided pursuant to an agreement with the Agency.

Attached is also a list (Exhibit B) of major health effects studies on pesticides conducted by IBT identifying which have been found valid or invalid, and which have been or are in the process of being replaced. This list covers 801 studies on 140 pesticides. An earlier draft list of IBT tests prepared by EPA in May 1983 identified 1205 tests on 212 pesticides. The current list has eliminated duplicative entries, preliminary range finding and similar tests which were not true health effects studies, and short-term, acute toxicity tests which generally do not create a significant data gap and which will be replaced if needed, through the existing reregistration program described above. Thus, the current list of 801 studies covers health effects considered significant to regulatory decisions, such as induction of benign or malignant tumors (oncogenicity), birth defects (teratogenicity), genetic mutations, other adverse reproductive effects, and neurotoxicity. Of the 801 IBT studies in the pivotal categories, 594 (74%) have been found invalid. To date, of the invalid studies, 212 (36%) studies have been replaced or are in progress, 38 (7%) are under discussion for possible replacement, and 45 (7%) are of a type no longer required for registration.

One way to assess the impact of IBT is to consider the effect of invalid studies on the data base supporting pesticides used in high volume. Although hundreds of pesticides are registered, only 25 insecticides account for 85% of the actual pounds of insecticides used, 32 herbicides account for 82%, and only 8 fungicides account for 71% of the volume of those products used. Of these 65 most heavily used pesticides, only 18 have IBT data in one or

more important categories. Of those 18, all but one also have non-IBT data available in some or all of the same cagetories. The exception, prometon, a herbicide not used on food crops, has one partially valid IBT study and many non-IBT acute and subacute studies. Sixteen of these high volume chemicals are the subject of one of the regulatory procedures described above requiring additional data. Thus, the data bases for the high volume chemicals to which people are most likely to be exposed are for the most part unaffected by the IBT situation, and where there is an impact, EPA has taken active regulatory steps to obtain replacement data.

The principal remaining task of the IBT program is to clarify the status of the invalid studies for which registrants have indicated they do not intend to provide replacements, or have not communicated an intention one way or the other to EPA. Although around 300 studies are in this category, a significant number (140) of negative and non-responses involve discontinued or cancelled products, or pesticides of such low volume use that registrants may choose not to invest in further testing needed to maintain registrations. The replacement status column of Exhibit B indicates that there are 159 invalid studies (26% of invalid IBT tests) for which there is negative or no response. However, as previously noted, most of these chemicals have non-IBT data available. Exhibit A shows that only five chemicals still registered and actually used have entirely IBT data bases. The 17 studies involved with those 5 chemicals constitute 3% of invalid IBT studies. A registration standard will result in replacement of 6 of these studies. This leaves only 11 studies or 2% of the invalid IBT tests which constitute the sole support of registered pesticides, and for which no regulatory action to generate replacement data has yet been initiated. Several of these 11 are valid or have at least supplementary value.

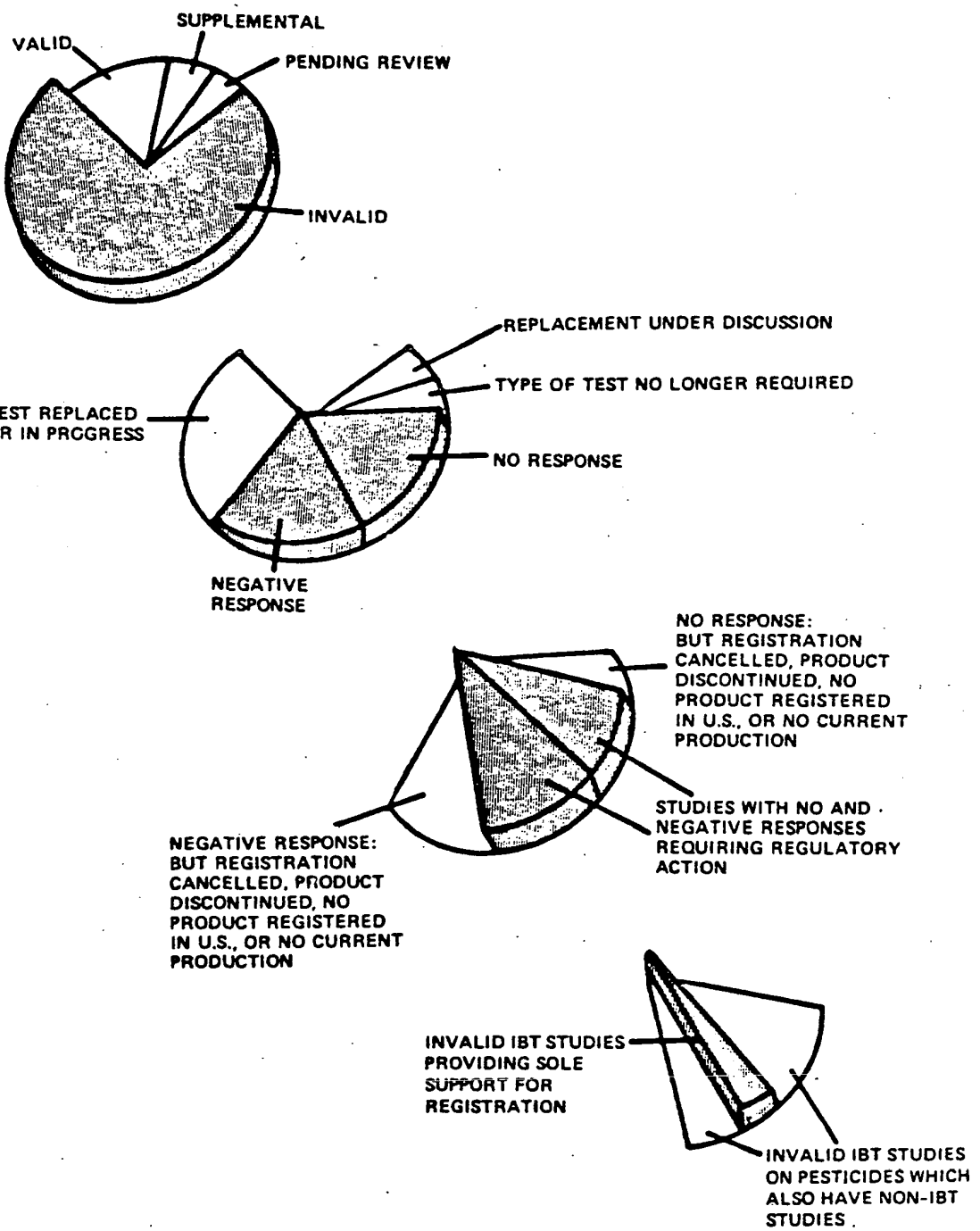
This report is being furnished to the registrants of the affected chemicals for which negative or no responses have been received concerning replacement of invalid IBT studies. We are also sending the registrants 3(c)(2)(B) notifications which require a registrant to make a specific commitment within 90 days or the registration may be suspended. In some cases, EPA and a registrant may agree that a specific study does not need to be replaced.

The IBT case caused serious concern and uncertainty about the potential hazards of the hundreds of pesticides involved, both for EPA and the public. Although it was advocated by some that all 212 pesticides tested in whole or in part by IBT be removed from the market pendihg retesting, that option is not available under current law.

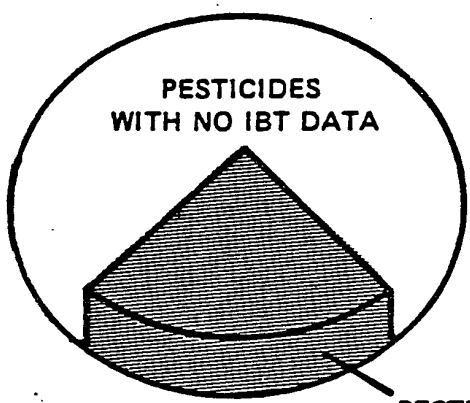
The regulatory response authorized by FIFRA requires valid evidence of risk, as opposed to a lack of information, before removing a product from the market, and allows for the replacement of inadequate data. As we reach the final resolution of the IBT problem, it appears that this approach was appropriate and adequate to deal with this event.

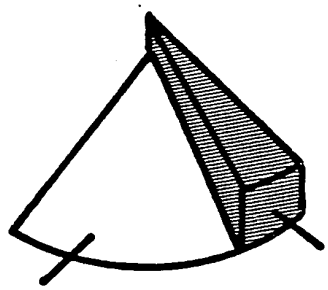
The IBT scandal shook the industry and government regulators. Obviously, steps had to be taken, not just to deal with the IBT situation itself, but to ensure that data providing the foundation of regulatory decisions in the future are adequately prepared and scrutinized. Thus, another result of the IBT case was the establishment in 1977 of a joint EPA-FDA audit program to help ensure that another IBT situation has not occurred and will not in the future. The lab audit program includes visits to laboratories to inspect their procedures, facilities and staff qualifications, and about sixty audits per year of labs and/or individual pesticide studies to see if the reported results are supported by the "raw" laboratory records and data. In the past six years, we have found the large majority of laboratories to be in compliance with current standards, and producing scientifically valid studies. An important effect of the IBT case has been to make the testing community, the industries which use their services, and government regulators keenly aware of the need to maintain high standards of quality control over health effects testing.

EPA ASSESSMENT OF THE 801 MAJOR IBT TESTS



EPA ASSESSMENT OF EFFECT OF IBT DATA ON 65 LARGEST USE PESTICIDES*





*25 INSECTICIDES ACCOUNTING FOR 85% OF POUNDAGE USED, 32 HERBICIDES ACCOUNTING FOR 82% OF POUNDAGE USED, AND 8 FUNGICIDES ACCOUNTING FOR 71% OF POUNDAGE USED, IN 1980.

SUMMARY STATISTICS: IBT

TOTALS

38	COMPANIES
140	CHEMICALS
801	STUDIES

STUDY VALIDATION STATUS

131	16%	VALID
44	6%	SUPPLEMENTAL
32	4%	PENDING
594	74%	INVALID
801	100%	

INVALID STUDY REPLACEMENT STATUS

212	36%	STUDY REPLACED OR IN PROGRESS
38	6%	REPLACEMENT UNDER DISCUSSION
45	8%	STUDY NO LONGER REQUIRED
116	20%	NEGATIVE RESPONSE BUT PRODUCTS ARE CANCELLED, DISCONTINUED, NOT REGISTERED IN THE U.S., OR HAVE NO PRODUCTION.
24	4%	NO RESPONSE BUT PRODUCTS ARE CANCELLED, DISCONTINUED NOT REGISTERED IN THE U.S., OR HAVE NO PRODUCTION.
86	14%	NEGATIVE RESPONSE AND INVALID
73	12%	NO RESPONSE AND INVALID
594	100%	

IBT STUDIES PROVIDING SOLE SUPPORT FOR REGISTRATION

17	3%	IBT STUDIES PROVIDE SOLE SUPPORT FOR REGISTRATION
−6	1%	CHRONIC STUDIES GENERATED BY REGISTRATION STANDARD
11	2%	

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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ADDITIONAL BACKGROUND ON THE IBT REVIEW PROGRAM

In 1976, during a routine lab inspection of one of IBT's facilities, FDA discoverd deficiencies in the manner in which studies were being conducted and discrepancies between those studies and their raw data. In 1977, EPA placed a moratorium on registration actions involving data developed at IBT as a result of this information. In the same year, EPA notified registrants that they were required to audit the raw data and validate both those IBT studies which were pivotal to the data base of pesticides already registered and all those which were supporting new registration actions.

In 1978 a joint EPA/FDA audit of IBT's two other facilities uncovered problems similar to those discovered during the initial audit. In March of that year EPA required registrants to submit to EPA the raw data for the IBT studies so that a review of registrant audits could be conducted.

EPA referred this case to the Department of Justice for investigation in April 1978. At approximately the same time, the U.S. and Canada were negotiating an agreement to share the task of spot checking registrants' audits of IBT studies. Through these checks, however, it became apparent that registrants' audits routinely overlooked some areas of concern. As a result, Canada and the U.S. agreed to review each audit and study.

Mutual agreement was reached as to which studies would be reviewed by each country. It was also decided that each country would accept the other's determination as to validity. However, due to differences in data requirements, each country would independently evaluate whether studies met their regulatory requirements, and determine the need for replacement studies.

After two years experience of the review program a decision was made to reconsider past policies regarding IBT data. A policy statement reflecting decisions made as a result of this analysis was sent to registrants in July 1980. The decisions were: 1) that the moratorium on registration actions was lifted unless a valid IBT study was essential to the approval of a specific action, 2) that registrants would be required to fill data gaps resulting from invalid IBT studies, 3) minor data gaps would be considered through normal registration channels, 4) if the entire data base was invalid, EPA would consider cancellation action, and 5) if previously unreported adverse effects were discovered, the study would have to be replaced, and in addition the Agency would consider initiating either an intensive risk/benefit review, or formal hearings on a chemical's registration status.

The IBT Review Program consisted of validation review, evaluation review, and data gap review. Validation review was designed to determine whether the information in the final report was supported by the raw data. Evaluation of whether a study met Agency guidelines for studies used to support registration, was performed on studies determined to be valid or at least reliable enough to supplement other valid data. Data gap review was a search through a chemical's entire data base to determine which invalid studies needed to be replaced.

Because our experience with data gap review proved it to be extremely time consuming, options for completing the IBT program more expeditiously were considered. As a result, several policy changes were adopted and conveyed to registrants in a letter in April 1982 which stated: 1) that acute IBT studies would no longer be reviewed through the IBT program. Instead, they would be reviewed through normal registration channels; 2) that studies which were considered invalid because the registrant initially chose not to audit them, would not be reviewed by the Agency and our presumption would be that they had to be replaced; 3) that EPA would no longer perform a data gap review of a chemical's data base to determine if other studies existed to replace the IBT studies, instead we would assume that replacement was necessary unless the registrant could convince us otherwise; and 4) that EPA would not review an IBT study if the registrant identified a replacement and agreed to have the IBT study considered invalid.

The review stage of the IBT program is essentially complete. The remainder of the program consists of obtaining replacement studies and tracking commitments to replace studies.

EXHIBIT A

THE DATA BASE FOR INDUSTRIAL BIO-TEST CHEMICALS

Exhibit A quantitatively presents the data base of the chemical compounds for which studies were conducted by Industrial Bio-Test Laboratories. The IBT studies are designated by the letter O. Studies in the EPA data base done by labs other than IBT are designated by the letter X.

The studies are arrayed across six categories of chronic effects. These chronic effects are: oncogenicity, teratogenicity, mutagenicity, reproductive effects, neurotoxicity, and other chronic effects.

Some of the chemicals in this exhibit appear to have no IBT studies because the studies conducted for these chemicals by IBT were all in the acute categories. The chemical names used are those that were listed in the IBT records. There is no designation of the validity or invalidity of the IBT studies presented. Specific information of this nature is in Exhibit B.

Exhibit A also notes any ongoing regulatory activity that will generate chronic data for these chemicals. The types of regulatory activity that cause the generation of data are: the registration standard program, the data call in program, the rebuttable presumption against registration program, and any special action employing the 3c2b provision of the Federal Insecticide, Fungicide, Rodenticide Act. There are approximately 2830 chronic studies indicated in this data base.

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Accel		X					
Alanap		X	X	X		XX	
Alar	X	XX O	XX	X		X	Registration Standard
Ametryn			XXX	O		OOO	Data Call In
Asulam	XXX	XX	XXX	X			Data Call In
Atrazine	X	XX	XXXXXXX	XX		XXX OO	Data Call In
Avadex	XXXX	XX O	XXX O	O	O	X OO	Registration Standard
Avenge	XXX	X	X	XX		XXX	Data Call In
Azodrin		X	XXXXXX	XXXX	XXXXXXX	XXX	Data Call In
Bacillus.thurin				X		XXXXX	Data Call In

O = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Barban			XX			X 000	**Data Call In**
Bardike		X					
Baygon	XX	XX	XXXXX 0	X	XXXXXXXXX XXXXXX	XXX	
Bifenox		0	0	0		00 000	**Registration Standard**
Binapacryl			0	0		00000	Not registered in U.S.A.
Bladex		X 00	XX			XXX	**Data Call In**
Bolero (thiobencarb)	XX	X 00	XXX 00	XXXXXXX 0	X 00	XX 0000	
Brodifacoum (Talon)		X					
Busan 74			XXXXX				
Bux		00	X		X 0	X 0	**Data Call In** Not registered in U.S.A.

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Captan	XXXXX 00	XXXXXXX 000000	XXXXXXXXX 000	XXX 00		XXX	
Carbaryl	XXXXXXX	XXXX	XXXX	XXXXXX	XXXXXXXXXX XXXXXXXX 0	XXXX	RPAR 3c2b
Carbofuran	XXXXX 00	XXXX 0	X 00	XXX 00000	XXXX 00000	XXXX 000	Data Call In
CGA-12223	0	XXX	XX	XX 0	X 00	000	Not marketed in U.S.
Chipco-RP26019	X	XX	XXX	XXXX		X	
Chlorobenzilate	X			X		XXXXXXXX	RPAR Data Call In
Chloropropham	XXXX	XXX	XX	X 00	X 0	XX 0	Data Call In
Chlorothalionil	XXX	XX	XXXXXXXXX	XXXX		XXXXXX	Data Call In
Chloropyrifos	X	XX		XXX	X=30	XXXX	Data Call In
Chloropropylate				X		X	Data Call In Discontinued Product

IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Cidial, Phenthoate Dimethoate	0	0	X 00	00	XX 0	X	RPAR Registration Stnd
Ciodrin	X		XX		XXXXXXXX		
Cobex	00	0				000	Data Call In-suspended
Coral		X		X 00	X=20 0	XXXXXX	Registration Standard
Curacron (Profenofos)	XX 0	XX	XX	XXXXXXX 0	XXXXXX 00	XXX 0	
Cycle		X				X 0000	Discontinued Product
Cycocel	X		X			X	
Cyprazine	0						Data Call In Discontinued Product
Dasanit		X 0	0	X	XXXXXXXXX XXXXXX	XX	Data Call In
DCPA			XXXX	XXX 0		XX	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Delnav	XX			0	XXXXXXXXX XXXXXX	XXX	Data Call In
Desmedipham		00	X		0		
Diazinon	XXX 0	XXXXX	XXXXXX	XXX	X=36	XXXXXX	Data Call In
Dicamba	0	XXXXX 0	X 000	XXX 0		XXXX	Data Call In
Dichlobenil						XX 00	Data Call In
Difolatan	X	00000000	XX	XXXX 000			Data Call In
Dinoseb		X 0	X	X		XX	
Diquat	X	XXX	XXX	X 00		XXXX 0	
Disyston		X 0	XX 0	XX	X=19 0		Data Call In
Dowco 233	XX	XXXX	XXXXX	XXX		0	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Dowco 290	X	X	X	O			
Drepanon		O		O		0000	Not Registered
Embark	X	X		X	X	XX	
Endothall	XXX O	XXXXXX	XXXXXXXX	XX		XXXX	
EPN	XX		X	X	X=30 0000		RPAR
Ethiolate		OO			OO		Discontinued Product
Ethion	O	X O	XX O	O	XXXXXXXXX OO		Data Call In
Fenvalerate	XX	XXXX	XXXXXXXXX	XXXXXXXXX X	X=24	X=23	Data Call In
Fenitrothion	X	X	XX	XX	X=20	XXX	
Fluroridamid		X					

O - IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Folpet	XX	XXXXXX 00000	XXXX 0	00		X 00	Data Call In
FormetanateHCL		X 0	X 0	0	000000	00	Data Call In
Furloe (Chloropropham)	XXXXXX	XXXX	XXXX	XX 0	X	XXX	
Glutaraldehyde		0	X				Ultra minor non food use
Glyphosate	0	XX 000	X 0000	XXX 00	0	XX	Data Call In
Glyphosine	0	0	0	0	00	00	
Gossyplure			X				Data Call In
Heptachlor Epox	XXXXXXXX XX	XXXXX	XXXXX	XXXXXXXX 0	X	XXXXXXXX XXXXXX	All uses cancelled
Hinosan		X	0		XX		
Irgasan	00	X 0	XXXXXXXX XXXX	X 00		XX 0	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Krenite		X		X			
Lasso	X O	XXX O	XXX OOOOO	X O		XX OO	Data Call In
Lorox		XX	XX	XXX		XXXXX	
Machete	O	X O	XXXXXX OOOO	XXXXXX OO	X	OOO	Data Call In
Maleic Hydra.	XXXXXX	X	XXXXX	X		XX	Data Call In
MCPA		XXXXXXXX	XXX	XX		X	Registration Standard
MCPP		XXXXX		X			
Merphos					XXXXXX		
Mesurol			X O	XXX O	XXXXXXXX XXXX OO	XXXXXXX	
Meta-Systox R		X O	O	X	XXXXXXXX XXX	XX OO	

O - IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Metobromuron				0		0000	Not registered in U.S.A.
Methazole	00	X	X 000	XXXXXXXX 0		00000	Data Call In
Methomyl	XXXXXX	XX	XX		XXXXXXXXX XX	XXXXXX	Registration Standard
Methoprene	XX	XXXXX 00	XX	XXXXXXXXX 0		XXXX	Registration Standard
Metolachlor	X 0	XX	XX	X 0		XXX 0	Registration Standard
Mocap (Ethoprop)		X	X		XX	0	
Monitor (Methamidophos)		X 00	X 0	XX 0	X=11 0=7	00	Registration Standard
Morestan	X	X	0	X 0		XXX	
Naled		X 0	XX	0	XXXXXX 000	00000	Data Call In
Nemacur	X 0	0	X 0	X	XXXXXXXX	XXXX	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Nemagon	X					XX	
Nemefene	XXX	0	XXXX	00		X 0	
Norea				0		000	Data Call In
Omadine		XXXXXXX 00000000	X 00	X	XXXXX	XX 000	Discontinued Product Data Call In
Omite-Comite	X	XXXX 0	X	X	0	XX	
Orthene (Acephate)	XXXX 0	XX 00	X 0	XXXX 000	X=12 00000	XXXX 000	
Oxadiazon	X	XXXX	X=16		X	XXX	Data Call In
Paraquat	X	XXXXX	XXXXX	XXXXXXX	0	XXXX 0	Date Call In
PCNB	XXX	XXXXXX	XXXX	XXXX		X=14	
Penncap E (ethyl parathion)	XX	X	XX	XX	X=37 0	X	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Penncap M. (methyl parathion)			XX	XXX	X=22	XXX 0	
Permethrine	X=11	XXXXXXX	X=23	X=13	X=21	X=12	Data Call In
Phorate		X	XX	X	X=16 0		Data Call In
Phosalone	X	XXXX	XX	XXX	X=12	X	Registration Standard
Phosphamidon				000	XXXXXXX 000000	0	Data Call In
Picloram	X	XX 0		XXX		X 000	Data Call In
Pik Off	X 0	0	0	0		0	Not Registered
Piperonyl Butoxide	X	XXXXX 0		X	XXX	X=9	Data Call In
Plictran	X	XX		XXX		X=9	
Polyram	XXX	X		XX 0		X 000	Data Call In

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
PPG 124			X				
Profluralin	X	O		X		X	Data Call In
Prometon		O					
Prometryn		X	X	XX		X	
Propham	XXXXXX	XXX	XXXX	X	O		
Prowl	XXXXX	X OO	XXX	XXXXXX		XXXX O	Data Call In
Pyrethrin	X	XX		XXXXXX	XXXXX	X=10 O	
Rabon	XXX	O	XXXXX	XXXXX	XXX	XXXXXXX	
Ramrod	O	X OO	X O	OO		OOO	
Randox		O	X O	O		O	

O = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Resmethrin	XXXX	XXXXXX 000	XXXX	XXX	XXXX	XXXXX	
Ronnel		XX 0		XXX	X=25	XX	Discontinued Product
Rydex (Prodiamine)	X 0	0	0	0		0000	Not Registered
Santophen		X 00	0	0			No Food Use
Sectrol	X	XXXXXXX	X	X=9	X=9	X=20 0	
Sencor	X 0	XXX 000	XXXXXXX 0	XX		XXX	
Simazine	XX 0	X	XX	XXX	X	XXXXXXX 0	Data Call In
Sodium Azide		0	XXXXX			XXX	
Sodium Bromide						X	
Sodium Chlorate				0		0	

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Sumitol		O					Discontinued Product
Supracide	X O		X=14	XX	X=26	XXXXX O	
Tedion			X	XXX O		XXXXXXXX	Data Call In Suspended
Terbufos	X	X O	XX	XXX	XXXXXX	XXXX	Data Call In
Terbuthylazine	X	O	XX	O		OO	Cancelled
Terbutryn		XX O	XXX	X		XXX	Data Call In
Terrazole	X	XXXXXX O	XX	XX		XXXXXXX	Registration Standard
Thidiazuron	O		X	O		O	
Thiodan	XXX	XX O	X O	O	XXXX O	XXXXXX OO	Registration Standard
Thiofanox		XX	X	XX	X=9 OO	XXX O	

O - IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Thiophanate	XX	XXX	X=10	XXXX	XX	XXXXXXXX	
Torak (dialifor)		000	X	0000	XXXXXX 000000	000	Registration Standard
Toxaphene	X			XXXX 0	XX 0	XXXX 00	RPAR
Triallate	X	X 0	XXXXXX 0	0	0	00	Data Call In
Triforine	X	XX	X 0	XX		XXXX	
Triphenyltin Hydr.	X	XXXXX		XXXXXX		X	
Vapona (DDVP)	X	XX	X=11	XX	X=70 0	XXXXXX	Data Call In
Velpar		XXX	X	XXXX		XXXXXX	Registration Standard
Vendex		XXX	XXX	XXXX	X	X=9	
Vinyzine				XX			

0 = IBT

CHEMICAL COMPOUNDS TESTED BY INDUSTRIAL BIO-TEST LABORATORIES:
A QUANTITATIVE PRESENTATION OF STUDIES SUBMITTED TO EPA BY IBT AND OTHER LABORATORIES.

CHEMICALS	ONCOGENICITY	TERATOGENICITY	MUTAGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY	OTHER CHRONIC EFFECTS	REGULATORY ACTIVITY TO GENERATE CHRONIC DATA
Visco 1152		XX	X			X	
Visco 1153		XX	X			X	
Vitavax	X	XXX	XXX			XXXXXX OO	
Vorlex	XXX	XX O	XXXX	O		X O	
Vydate (oxamyl)	X	XXXXX	XX	XXXXXXXX	X	XXX	
4-Amino-pyridine							Registration Standard
2,4-D		X=11	XXXXX	XXXXX		XXXX	Data Call In

O = IBT

EXHIBIT B

IBT TRACKING SYSTEM REPORT

IBT TRACKING SYSTEM REPORT

CODE DEFINITIONS

VALIDATE: a review designed to determine if the information in the final report was supported by the raw data from the study.

I - Invalid. The information in the final report was not supported by the raw data from the study.
P - Pending. The study is still under validation review.
S - Supplemental. Portions of the study are valid and can be used independently of the remainder of the study.
V - Valid. The information in the final report is supported by the raw data from the study.

EVALUATE: a review designed to determine if a study meets Agency guidelines for studies to be used in support of pesticide registration.

C, CM - Core minimum. The study meets the regulatory data requirements to support pesticide registration.
S, CS - Core supplemental. The study is useful to supplement other studies.
I, CI - Core invalid. The study does not meet the regulatory data requirements to support registration.
P - Pending. The study is still under evaluation review.
NA - Not applicable. The study was not given an evaluation status if the validation process determined it to be invalid.

REPLACE: the column indicating the replacement status of the study.

Replaced - Study replaced or in progress
Discussion - Replacement study under discussion
Not Req - Study no longer required
No Resp - No response from registrant
Neg Resp - Negative response from registrant

IBT TRACKING SYSTEM REPORT

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
B-1708	ALAR	UNIROYAL		TERATOLOGY	RAT	I	NA	REPLACED
B-4715	AMETRYN	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	DISCUSSION
C-4716	AMETRYN	CIBA GEIGY	ORAL	CHRONIC	DOG	I	NA	DISCUSSION
P-4709	AMETRYN	CIBA GEIGY		REPRODUCTION	RAT	I	NA	DISCUSSION
2945	AMETRYN	CIBA GEIGY	DERMAL		RAT/RABBIT	I	NA	NOT REQ
601-4274	ANTOR	BFC	DERMAL	SUBACUTE	RABBIT	V		NO RESP
611-8169	ANTOR	BFC	ORAL	SUBCHRONIC	DOG	V	P	REPLACED
622-0466	ANTOR	BFC	ORAL	SUBCHRONIC	RAT	P		NO RESP
622-3059	ANTOR	BFC	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
622-8166	ANTOR	BFC	ORAL	SUBCHRONIC	RAT	V		NO RESP
8560-10525	ANTOR	BFC	ORAL	CHRONIC	RAT	V		NO RESP
8580-08351	ANTOR	BFC	ORAL	CHRONIC	MOUSE	V	NA	NO RESP
8560-8350	ANTOR	BFC	ORAL		RAT	I	NA	NO RESP
622-6769	ATRAZINE	CIBA GEIGY	ORAL	CHRONIC	RAT	S		REPLACED
8580-8906	ATRAZINE	CIBA GEIGY	ORAL	CHRONIC	MICE	S		NO RESP
59-13	AVADEX	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	DISCUSSION
59-13A	AVADEX	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	DISCUSSION
59-13B	AVADEX	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	DISCUSSION
59-13C	AVADEX	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	DISCUSSION
622-5250	AVADEX	MONSANTO	ORAL	CHRONIC	RAT	I	NA	DISCUSSION
622-5252	AVADEX	MONSANTO		MUTAGENICITY	MOUSE	I	NA	DISCUSSION
623-6841	AVADEX	MONSANTO		REPRODUCTION	RAT	V	P	NO RESP
651-5254	AVADEX	MONSANTO		TERATOLOGY	RABBIT	I	NA	DISCUSSION
8530-9030	AVADEX	MONSANTO		CHOLINESTERASE	RAT	V		NO RESP
8580-10580	AVADEX	MONSANTO	ORAL	CHRONIC	DOG	P	NA	NO RESP
8532-10762	AVADEX	MONSANTO	ORAL		MOUSE	P		NO RESP
8580-10813	AVADEX	MONSANTO	NEURO		HEN	V	P	NO RESP
8580-9119	AVADEX	MONSANTO	NEURO		HEN	V	P	NO RESP
	AVADEX	MONSANTO	ORAL		RAT	I	NA	REPLACED
	AVADEX	MONSANTO	ORAL		DOG	I	NA	NEG RESP
B-2793	BACILLUS THURING	SANDOZ	ORAL	SUBACUTE	RAT	V	NA	REPLACED
B-585	BARBAN	VELSICOL	ORAL	CHRONIC	RAT	I	NA	REPLACED
C-721	BARBAN	VELSICOL	ORAL	CHRONIC	DOG	I	NA	REPLACED
1017	BARBAN	VELSICOL	ORAL	CHRONIC	RAT	I	NA	REPLACED
563	BARBAN	VELSICOL	ORAL		RAT	I	NA	REPLACED
E-8917	BAYGON	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
A-5372	BENZADOX	GULF	DERMAL	SUBACUTE	RABBIT	I	NA	NO RESP
B-4381	BENZADOX	GULF	ORAL	SUBACUTE	RAT	I	NA	NO RESP
C-4382	BENZADOX	GULF	ORAL	SUBCHRONIC	DOG	I	NA	NO RESP
A-1884	BIFENOX	MOBIL	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-1474	BIFENOX	MOBIL	ORAL	SUBCHRONIC	RAT	V	P	NO RESP
B-2156	BIFENOX	MOBIL		TERATOLOGY	RAT	V	P	NO RESP
C-1475	BIFENOX	MOBIL	ORAL	SUBCHRONIC	DOG	V	P	NO RESP
E-2155	BIFENOX	MOBIL		MUTAGENICITY	MOUSE	I	NA	NEG RESP
J-1548	BIFENOX	MOBIL		CATARACTEGEN	HEN	I	NA	NEG RESP
J-782	BIFENOX	MOBIL		CATARACTEGEN	HEN	I	NA	NEG RESP
621-5532	BIFENOX	MOBIL	ORAL	CHRONIC	DOG	V	P	NO RESP
621-5533	BIFENOX	MOBIL	ORAL	CHRONIC	RAT	I	NA	NEG RESP
623-6793	BIFENOX	MOBIL		REPRODUCTION	RAT	V		NO RESP
8530-8513	BIFENOX	MOBIL	DERMAL	SUBACUTE	RABBIT	V	P	NO RESP
8580-9571	BIFENOX	MOBIL	ORAL	SUBACUTE	QUAIL	I	NA	NO RESP
	BINAPACRYL	FMC	ORAL	CHRONIC	CAT	P	NA	NEG RESP
	BINAPACRYL	FMC	ORAL	SUBCHRONIC	RAT	P	NA	NEG RESP
	BINAPACRYL	FMC	ORAL	SUBCHRONIC	DOG	P	NA	NEG RESP
	BINAPACRYL	FMC	PERCUTAN	SUBACUTE	RABBIT	P	NA	NEG RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
B-2210	BINAPACRYL	FMC	ORAL	CHRONIC	RAT	I	NA	NEG RESP
B-2705	BINAPACRYL	FMC		REPRODUCTION	RAT	I	NA	NEG RESP
C-1426	BINAPACRYL	FMC		CATARACTEGEN	HEN	I	NA	NEG RESP
C-2209	BINAPACRYL	FMC	ORAL	CHRONIC	DOG	I	NA	NEG RESP
OFF1	BINAPACRYL	FMC	ORAL		DOG	I	NA	NEG RESP
J-238	BLADEX	SHELL		TERATOLOGY	RABBIT	I	NA	REPLACED
8530-11112	BLADEX	SHELL		TERATOLOGY	RABBIT	I	NA	REPLACED
B-353	BOLERO	CHEVRON	ORAL	SUBACUTE	RAT	I	NA	REPLACED
C-610	BOLERO	CHEVRON	ORAL	SUBACUTE	DOG	I	NA	REPLACED
601-5223	BOLERO	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
621-2095	BOLERO	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
621-4652	BOLERO	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
622-2440	BOLERO	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
622-2440	BOLERO	CHEVRON		TERATOLOGY	RAT	I	NA	REPLACED
622-5225	BOLERO	CHEVRON		MUTAGENICITY	MOUSE	I	NA	REPLACED
651-2096	BOLERO	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
651-5143	BOLERO	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
651-5265	BOLERO	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
8533-10026	BOLERO	CHEVRON		MUTAGENICITY	MOUSE	I	NA	REPLACED
651-7433	BOLERO	CHEVRON			HEN	V	V	NEG RESP
8580-10025	BOLERO	CHEVRON	NEURO		HEN	S	S	REPLACED
C-6581	BROMOPHENOXIM	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
B-5433	BROMOPROPYLATE	CIBA GEIGY	ORAL	CHRONIC	RAT	P		NEG RESP
622-5433	BROMOPROPYLATE	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	NEG RESP
622-6724	BROMOPROPYLATE	CIBA GEIGY		REPRODUCTION	RAT	P		NO RESP
622-6726	BROMOPROPYLATE	CIBA GEIGY		CARCINOGENICITY	MOUSE	S	S	NEG RESP
8531-9996	BROMOPROPYLATE	CIBA GEIGY		CHOLINESTERASE	DOG	I	NA	NEG RESP
B-7120	BUSAN 74	BUCKMAN	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
C-7121	BUSAN 74	BUCKMAN	ORAL	SUBCHRONIC	DOG	V		NO RESP
611-03366	BUTAM	GULF	ORAL	SUBACUTE	DOG	I	NA	NOT REQ
622-03363	BUTAM	GULF	ORAL	SUBACUTE	RAT	I	NA	NOT REQ
A-8995	BUTYLTIN OXIDE		DERMAL	SUBCHRONIC	RABBIT	I	NA	NO RESP
A-3886	BUX	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
A-4407	BUX	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-3422	BUX	CHEVRON	ORAL	SUBCHRONIC	DOG	I	N	NEG RESP
B-3653	BUX	CHEVRON	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
B-4130	BUX	CHEVRON		CHOLINESTERASE	RAT	I	NA	NEG RESP
B-4339	BUX	CHEVRON		REPRODUCTION	RAT	I	NA	NEG RESP
C-3655	BUX	CHEVRON	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
J-4330	BUX	CHEVRON		DEMYELINATION	HEN	I	NA	NEG RESP
J-5536	BUX	CHEVRON		TERATOLOGY	RAT	I	NA	
J-5863	BUX	CHEVRON		TERATOLOGY	RABBIT	I	NA	NEG RESP
B-2804	CAPTAN	AMER/ SEED/CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-9267	CAPTAN	AMER SEED/CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-9271	CAPTAN	AMER SEED/CHEVRON		CARCINOGENIC	MOUSE	I	NA	REPLACED
J-139	CAPTAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-5420	CAPTAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	NO RESP
J-5438	CAPTAN	AMER SEED/CHEVRON		PROGENY	DOG	I	NA	NO RESP
P-5397	CAPTAN	AMER SEED/CHEVRON		TERATOLOGY	RAT	I	NA	NO RESP
P-5398	CAPTAN	AMER SEED/CHEVRON		TERATOLOGY	RABBT/HAMSTR	I	NA	REPLACED
P-5570	CAPTAN	AMER SEED/CHEVRON		MUTAGENICITY	MOUSE	I	NA	REPLACED
BCRF-139	CAPTAN	AMER SEED/CHEVRON		REPRODUCTN	CHICKEN	I	NA	NOT REQ
621-5519	CAPTAN	AMER SEED/CHEVRON		TERATOLOGY	MONKEY	I	NA	NO RESP
622-5998	CAPTAN	AMER SEED/CAPTAN		DOMINANT LETHAL	MOUSE	I	NA	NO RESP
623-5998	CAPTAN	AMER SEED/CHEVRON		DOMINANT LETHAL	MOUSE	I	NA	NO RESP
8530-9030	CARBARYL	MONSANTO		CHOLINESTERASE	RAT	V	P	NO RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
A-7099	CARBOFURAN	FMC	ORAL	SUBACUTE	RABBIT	I	NA	NOT REQ
A-972	CARBOFURAN	FMC		CHOLINESTERASE	RAT	I	NA	REPLACED
B-1590	CARBOFURAN	FMC	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
B-1591	CARBOFURAN	FMC	ORAL	SUBCHRONIC	RAT	I	NA	NOT REQ
B-3113	CARBOFURAN	FMC	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
B-3637	CARBOFURAN	FMC	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-3638	CARBOFURAN	FMC		REPRODUCTION	RAT	I	NA	REPLACED
B-400A	CARBOFURAN	FMC		CARCINOGENICITY	MOUSE	I	NA	REPLACED
B-4443	CARBOFURAN	FMC		CHOLINESTERASE	RAT	I	NA	REPLACED
B-6845	CARBOFURAN	FMC	ORAL	SUBACUTE	RAT	I	NA	REPLACED
B-973	CARBOFURAN	FMC		CHOLINESTERASE	RAT	I	NA	REPLACED
C-3636	CARBOFURAN	FMC	ORAL	CHRONIC	DOG	I	NA	REPLACED
C-4442	CARBOFURAN	FMC		CHOLINESTERASE	DOG	I	NA	REPLACED
E-401A	CARBOFURAN	FMC		MUTAGENICITY	RAT	V	CI	REPLACED
E-401B	CARBOFURAN	FMC		MUTAGENICITY	MOUSE	V	CI	REPLACED
J-5145	CARBOFURAN	FMC		TERATOLOGY	RABBIT	I	NA	REPLACED
J-6296	CARBOFURAN	FMC		REPRODUCTION	DOG	V	P	NO RESP
N-5183	CARBOFURAN	FMC	INHALATION	SUBACUTE	GUINEA PIG	I	NA	REPLACED
P-4387	CARBOFURAN	FMC		REPRODUCTION	RAT	I	NA	REPLACED
P-4802	CARBOFURAN	FMC		REPRODUCTION	RAT	I	NA	REPLACED
P-6315	CARBOFURAN	FMC		REPRODUCTION	RAT	I	NA	REPLACED
3891	CARBOFURAN	FMC	PERCUTAN	SUBACUTE	RABBIT	I	NA	NOT REQ
J-5144	CARBOFURAN	FMC	NEURO		HEN	I	NA	NOT REQ
622-5121A	CGA-12223	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
623-07922	CGA-12223	CIBA GEIGY		REPRODUCTION	RAT	I		NO RESP
8531-09995	CGA-12223	CIBA GEIGY		CHOLINESTERASE	DOG	V	S	NOT REQ
8532-07921	CGA-12223	CIBA GEIGY		CARCINOGENIC	MOUSE	P		NO RESP
611-5122A	CGA-12223	CIBA GEIGY	ORAL		DOG	S	S	REPLACED
8532-10607	CGA-12223	CIBA GEIGY	ORAL		RAT	P		NO RESP
8580-10767	CGA-12223	CIBA GEIGY	NEURO		HEN	S	S	NO RESP
C-6785	CHLORBROMURON	CIBA GEIGY		METHEMOGLOBIN	CAT	I	NA	NEG RESP
A-5253	CHLORBROMURON	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
B-5262	CHLORBROMURON	CIBA GEIGY	ORAL		RAT	I	NA	NEG RESP
C-5264	CHLORBROMURON	CIBA GEIGY	ORAL		DOG	I	NA	NEG RESP
A-3512	CHLOROBENZILATE	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
A-4646	CHLOROBENZILATE	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
90104	CHLOROPICRIN		ORAL	SUBACUTE	RAT	I	NA	NO RESP
P-5821	CHLOROPROPHAM	PPG		REPRODUCTION	RAT	I	NA	REPLACED
623-05515	CHLOROPROPHAM	PPG		REPRODUCTION	RAT	P		NO RESP
651-05514	CHLOROPROPHAM	PPG	ORAL	CHRONIC	MOUSE	P		NO RESP
C-4645	CHLOROPROPYLATE	CIBA GEIGY	ORAL	CHRONIC	DOG	I	NA	NEG RESP
663-3477	CHLOROTHALONIL	DIAMOND SHELL	INHALATION	SUBACUTE	RAT	I	NA	DISCUSSION
B-8829	COBEX	US BORAX	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
B-9341	COBEX	US BORAX		CARCINOGENIC	RAT	I	NA	REPLACED
E-339	COBEX	US BORAX		MUTAGENICITY	MOUSE	V		NO RESP
J-8994	COBEX	US BORAX		TERATOLOGY	RABBIT	I	NA	REPLACED
J-9081	COBEX	US BORAX		CATEROGEN	CHICKEN	I	NA	REPLACED
J-9402	COBEX	US BORAX	DERMAL	CARCINOGEN	MOUSE	I	NA	REPLACED
A-1062	COBEX	US BORAX	DERMAL	TOX	RABBIT	I	NA	NEG RESP
C-8830	COBEX	US BORAX	ORAL		DOG	I	NA	NEG RESP
J-105	CORAL	CHEMAGRO		DEMYELINIATION	HEN	I	NA	REPLACED
J-2570	CORAL	CHEMAGRO		REPRODUCTION	HEN	I	NA	DISCUSSION
17838	CORAL	CHEMAGRO		REPRODUCTION	HEN	I	NA	DISCUSSION
611-5122B	CURACRON	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	V	CM	REPLACED
611-5922A	CURACRON	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	V	NA	NO RESP
622-5121B	CURACRON	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	V	CM	REPLACED
622-6895	CURACRON	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	REPLACED

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
622-7923	CURACRON	CIBA GEIGY		CARCINOGENICITY	MOUSE	S		NEG RESP
623-7924	CURACRON	CIBA GEIGY		REPRODUCTION	RAT	V	CM	REPLACED
8531-09996-1	CURACRON	CIBA GEIGY		CHOLINESTER	DOG	P		REPLACED
8531-9996(A)	CURACRON	CIBA GEIGY		CHOLINESTERASE	DOG	P		NO RESP
8580-10426	CURACRON	CIBA GEIGY	NEURO		HEN	V	CM	NO RESP
8580-11187	CURACRON	CIBA GEIGY	NEURO		HEN	S	CS	DISCUSSION
C-3595	CYCLE	CIBA GEIGY	ORAL		DOG	I	NA	NEG RESP
611-03715	CYCLE	CIBA GEIGY	ORAL		DOG	I	NA	NEG RESP
622-03594	CYCLE	CIBA GEIGY			AT	I	NA	NEG RESP
622-03719	CYCLE	CIBA GEIGY	ORAL		RAT	I	NA	NEG RESP
A-295	CYPRAZINE	GULF	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
B-304	CYPRAZINE	GULF		TERATOLOGY	RAT	V		NO RESP
B-6277	CYPRAZINE	GULF	ORAL	SUBACUTE	RAT	P		NO RESP
B-9889	CYPRAZINE	GULF		CARCINOGENICITY	RAT	I	NA	REPLACED
C-6193	CYPRAZINE	GULF	ORAL	SUBCHRONIC	DOG	I	NA	REPLACED
C-9148	CYPRAZINE	GULF	ORAL	SUBACUTE	DOG	V	CI	NO RESP
C-9876	CYPRAZINE	GULF	ORAL	SUBACUTE	DOG	P		NO RESP
M-1275	CYPRAZINE	GULF	ORAL	SUBACUTE	RAT	P		NO RESP
A-3010	CYPROMID	GULF	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-3057	CYPROMID	GULF	ORAL		RAT	I	NA	NEG RESP
WCRF127	CYPROMID	GULF	ORAL		DOG	I	NA	NEG RESP
621-06998	D-PHENOTHRIN		ORAL	CHRONIC	RAT	I	NA	NO RESP
651-07001	D-PHENOTHRIN			TERATOLOGY	RABBIT	P		NO RESP
8533-07000	D-PHENOTHRIN			REPRODUCTION	RAT	V		NO RESP
8580-06999	D-PHENOTHRIN		ORAL		MOUSE	I	NA	NEG RESP
8537-9671	DANTOIN	GLYCO	DERMAL	SUBCHRONIC	RABBIT	S	S	NO RESP
E-8918	DASANIT	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	REPLACED
J-9028	DASANIT	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	DISCUSSION
601-4030	DC 5700	DOW/CORNING	DERMAL	SUBCHRONIC	RABBIT	I	NA	REPLACED
8533-10126	DC 5700	DOW/CORNING		TERATOLOGY	RAT	I	NA	REPLACED
8533-10127	DC 5700	DOW/CORNING		MUTAGENICITY	RAT	I	NA	REPLACED
F-1905	DC 5700	DOW/CORNING	PATCH TEST		HUMAN	I	NA	REPLACED
J-2369	DCPA	DIAMOND SHAMROCK		REPRODUCTION	HEN	I	NA	NOT REQ
663-3477	DCPA	DIAMOND SHAMROCK	INHALATION	SUBACUTE	RAT	I	NA	NOT REQ
P-2476	DELNAV	BFC		REPRODUCTION	RAT	I	NA	DISCUSSION
A-454	DESMEDIPHAM	NORAM	DERMAL	SUBACUTE	RABBIT	I	NA	DISCUSSION
A-455	DESMEDIPHAM	NORAM		CHOLINESTERASE	RAT	I	NA	DISCUSSION
B-396	DESMEDIPHAM	NORAM	ORAL	SUBACUTE	RAT	I	NA	DISCUSSION
B-585	DESMEDIPHAM	NORAM		TERATOLOGY	RAT	I	NA	DISCUSSION
C-1441	DESMEDIPHAM	NORAM	ORAL	CHRONIC	DOG	V		NO RESP
J-397	DESMEDIPHAM	NORAM	ORAL	SUBCHRONIC	DOG	I	NA	DISCUSSION
N-459	DESMEDIPHAM	NORAM	INHALATION	SUBACUTE	RAT	S	CS	DISCUSSION
650-7187	DESMEDIPHAM	NORAM		TERATOLOGY	RABBIT	I	NA	NEG RESP
B-1349	DIAQUAT		ORAL	CHRONIC	RAT	I	NA	NO RESP
D-4321	DIAZINON	CIBA GEIGY	ORAL	SUBACUTE	HUMAN	I	NA	NOT REQ
8580-9381	DIAZINON	CIBA GEIGY		CARCINOGENICITY	MOUSE	I	NA	NEG RESP
E-9892	DICAMBA	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
J-9012	DICAMBA	VELSICOL		TERATOLOGY	MOUSE	I	NA	REPLACED
623-7847	DICAMBA	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
633-7848/A	DICAMBA	VELSICOL		MUTAGENICITY	BACTERIA	I	NA	NEG RESP
651-3279	DICAMBA	VELSICOL		REPRODUCTION	HEN	I	NA	NOT REQ
8580-10130	DICAMBA	VELSICOL	ORAL	CHRONIC,CARCIN	MOUSE	P	NA	
	DICHLOBENIL	CASORAN	PERCUTAN	SUBACUTE		I	NA	NO RESP
B-2526	DICHLOBENIL	CASORAN	ORAL		RAT	I	NA	REPLACED

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
J-471	DISYSTON	CHEMAGRO	NEURO		HEN	I	NA	REPLACED
621-6138	DOWCO 233	DOW	ORAL	CHRONIC	RAT	S	S	REPLACED
C-2529	DICHLOBENIL	CASORAN	ORAL		DOG	I	NA	REPLACED
	DICHLOBENIL	CASORAN	PERCUTAN	SUBACUTE		I	NA	NO RESP
B-1254	DIFOLATAN	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-2804	DIFOLATAN	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-5397	DIFOLATAN	CHEVRON		TERATOLOGY	RAT	I	NA	REPLACED
C-1272	DIFOLATAN	CHEVRON	ORAL	CHRONIC	DOG	I	NA	NEG RESP
J-139	DIFOLATAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-3681	DIFOLATAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-5061	DIFOLATAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-5110	DIFOLATAN	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-5758	DIFOLATAN	CHEVRON		TERATOLOGY	HAMPSTER	I	NA	NEG RESP
M-5519	DIFOLATAN	CHEVRON		TERATOLOGY	MONKEY	V		NEG RESP
M-5519	DIFOLATAN	CHEVRON		TERATOLOGY	MONKEY	I	NA	NEG RESP
651-6459	DIFOLATAN	CHEVRON		REPRO & RESIDUE	HEN	I	NA	NEG RESP
P-8692	DINOSEB	VERTAC CHEM		TERATOLOGY	RAT	I	NA	NO RESP
B-1349	DIQUAT	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
8530-9549	DIQUAT	CHEVRON		REPRO & RESIDUE	HEN	P		NEG RESP
8580-8241	DIQUAT	CHEVRON		REPRO	DUCK	I	NA	REPLACED
8580-8242	DIQUAT	CHEVRON		REPRO	QUAIL	I	NA	REPLACED
8580-9546	DIQUAT	CHEVRON		REPRO & RESIDUE	HEN	V	NA	NEG RESP
E-8920	DISYSTON	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	REPLACED
J-9029	DISYSTON	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	REPLACED
623-3859	DOWCO 290	DOW		REPRODUCTION	RAT	I	NA	REPLACED
C-1441B	DREFAMON	MONTEDISON	ORAL	CHRONIC	DOG	V		NO RESP
621-1440	DREFAMON	MONTEDISON	ORAL	CHRONIC	RAT	I	NA	NO RESP
622-01442	DREFAMON	MONTEDISON		REPRODUCTION	RAT	P		NO RESP
651-7187	DREFAMON	MONTEDISON		TERATOLOGY	RABBIT	I	NA	NO RESP
B-1442	DREFAMON	MONTEDISON		2	RAT	P		NO RESP
C-1441A	DREFAMON	MONTEDISON	ORAL		DOG	V		NO RESP
611-7135	EMBARK	3M	ORAL	SUBCHRONIC	DOG	V		NO RESP
621-03115	ENDOTHALL	3M/PENWALT	ORAL	CHRONIC	RAT	I	NA	NO RESP
621-03463	ENDOTHALL	3M/PENWALT	ORAL	SUBACUTE	RAT	I	NA	NO RESP
J-7734	ENDOTHALL	3M/PENWALT			HEN	V	V	NEG RESP
J-8532	ENDOTHALL	3M/PENWALT			HEN	V	V	NEG RESP
8580-10332	EPN	DUPONT	NEURO		HEN	V		NO RESP
8580-10430	EPN	NISSAN/VELSICOL	NEURO		HEN	V	CM	NEG RESP
8580-10526	EPN	NISSAN/VELSICOL	NEURO		HEN	S	S	REPLACED
8580-8633	EPN	NISSAN/VELSICOL	NEURO		HEN	I	NA	REPLACED
B-304	ETHIOLATE	GULF		TERATOLOGY	RAT	I	NA	NEG RESP
B-305	ETHIOLATE	GULF		TERATOLOGY	RAT	V	P	NO RESP
B-9875	ETHIOLATE	GULF	ORAL	SUBACUTE	RAT	I	NA	NEG RESP
C-9876	ETHIOLATE	GULF	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
P-2461	ETHIOLATE	GULF		CHOLINESTERASE	RAT	I	NA	NEG RESP
P-2463	ETHIOLATE	GULF		CHOLINESTERASE	RAT	I	NA	NEG RESP
A-9040	ETHION	FMC	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
B-1056	ETHION	FMC		TERATOLOGY	RAT	I	NA	REPLACED
B-8706	ETHION	FMC	ORAL	CHRONIC	RAT	I	NA	REPLACED

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
B-5349	FORMETENATE HCL	NORAM		CHOLINESTERASE	RAT	I	NA	DISCUSSION
C-5346	FORMETENATE HCL	NORAM	ORAL	CHRONIC	DOG	I	NA	NOT REQ
C-8705	ETHION	FMC	ORAL	CHRONIC	DOG	V	P	NOT REQ
C-975	ETHION	FMC		CHOLINESTERASE	DOG	I	NA	REPLACED
E-1057A	ETHION	FMC		MUTAGENICITY	MOUSE	V	P	REPLACED
F-8948	ETHION	FMC		CHOLINESTERASE	HUMAN	V		NO RESP
M-9041	ETHION	FMC	DERMAL	SUBACUTE	MONKEY	I	NA	NOT REQ
2705	ETHION	FMC		REPRODUCTION	RAT	I	NA	REPLACED
621-01058	ETHION	FMC		CARCINOGENICITY	MOUSE	I	NA	REPLACED
J-1059	ETHION	FMC	NEURO		HEN	I	NA	REPLACED
J-5425	ETHION	FMC			HEN	V	P	NO RESP
C-1667	FENITROTHION			CHOLINESTERASE	DOG	I	NA	NEG RESP
C-9997	FENITROTHION		ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
F-9999	FENITROTHION		ORAL	SUBCHR&CHOLINEST	HUMAN	I	NA	NEG RESP
J-4052	FENITROTHION			REPRODUCTION	DUCK/QUAIL	V	P	NO RESP
J-9995	FENITROTHION			TERATOLOGY	RABBIT	I	NA	NO RESP
J-9996	FENITROTHION			TERATOLOGY	RABBIT	V		NO RESP
J-9998	FENITROTHION		ORAL	CHRONIC	DOG	V		NO RESP
621-7168	FENITROTHION		ORAL	CHRONIC	MONKEY	I	NA	REPLACED
8580-9445	FENITROTHION		NEURO		HEN	I	NA	NEG RESP
601-7889	FENUALERATE	SHELL	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
663-07419	FENUALERATE	SHELL	INHALATION	SUBACUTE	RAT	I	NA	REPLACED
B-5261	FLUORIDIFEN	CIBA GEIGY	ORAL		RAT	I	NA	NEG RESP
C-5263	FLUORIDIFEN	CIBA GEIGY	ORAL		DOG	I	NA	NEG RESP
A-3681	FOLPET	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
B-3566	FOLPET	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
C-7111	FOLPET	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
E-9099	FOLPET	CHEVRON		MUTAGENICITY	MOUSE	I	NA	REPLACED
J-139	FOLPET	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
J-5420	FOLPET	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
M-5519	FOLPET	CHEVRON		TERATOLOGY	MONKEY	I	NA	NEG RESP
P-5758	FOLPET	CHEVRON		TERATOLOGY	HAMPSTER	I	NA	NEG RESP
WCRF-152	FOLPET	NORAM		REPRODUCTION	RABBIT	I	NA	REPLACED
710	FOLPET	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
A-5344	FORMETENATE HCL	NORAM	DERMAL	SUBACUTE	RABBIT	I	NA	DISCUSSION
A-9144	FORMETENATE HCL	NORAM		CHOLINESTERASE	RAT	S	S	DISCUSSION
B-5345	FORMETENATE HCL	NORAM	ORAL	CHRONIC	RAT	I	NA	DISCUSSION
C-5350	FORMETENATE HCL	NORAM		CHOLINESTERASE	DOG	I	NA	DISCUSSION
D-6879	FORMETENATE HCL	NORAM		CHOLINESTERASE	DOG	I	NA	DISCUSSION
E-9145	FORMETENATE HCL	NORAM		PLACENTAL TRANS	RAT	I	NA	DISCUSSION
I-7144	FORMETENATE HCL	NORAM		CHOLINESTERASE	HUMAN	I	NA	DISCUSSION
J-9141	FORMETENATE HCL	NORAM		TERATOLOGY	RABBIT	I	NA	DISCUSSION
P-5347	FORMETENATE HCL	NORAM		REPRODUCTION	RAT	I	NA	DISCUSSION
P-9140	FORMETENATE HCL	NORAM		MUTAGENICITY	MOUSE	I	NA	DISCUSSION
E-5343	FORMETENATE HCL	NORAM	PATCH TEST		HUMAN	I	NA	DISCUSSION
J-5352	FORMETENATE HCL	NORAM	NEURO		HEN	I	NA	DISCUSSION
J-5354	FORMETENATE HCL	NORAM	DIETARY		PHES/DK/QUL	I	NA	DISCUSSION
P-5821	FURLOE	PPG		REPRODUCTION	RAT	I	NA	NO RESP
8533-9082	GLUTARALDEHYDE	3M		TERATOLOGY	RAT	I	NA	DISCUSSION

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
A-1549	GLYPHOSATE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	REPLACED
A-2144	GLYPHOSATE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	REPLACED
A-2468A	GLYPHOSATE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	REPLACED
B-1020	GLYPHOSATE	MONSANTO	ORAL	SUBCHRONIC	RAT	V	I	NO RESP
B-564	GLYPHOSATE	MONSANTO	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-566	GLYPHOSATE	MONSANTO		REPRODUCTION	RAT	V	I	REPLACED
B-569	GLYPHOSATE	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	REPLACED
C-1021	GLYPHOSATE	MONSANTO	ORAL	SUBCHRONIC	DOG	V	I	NO RESP
E-567	GLYPHOSATE	MONSANTO		MUTAGENICITY	MOUSE	I	NA	REPLACED
J-565	GLYPHOSATE	MONSANTO	ORAL	CHRONIC	DOG	V	I	NO RESP
J-568	GLYPHOSATE	MONSANTO		TERATOLOGY	RABBIT	I	NA	REPLACED
601-5044	GLYPHOSATE	MONSANTO	ORAL	SUBCHRONIC	RABBIT	I	NA	NOT REQ
601-6527	GLYPHOSATE	MONSANTO		CHOLINESTERASE	RAT	I	NA	NOT REQ
623-7508	GLYPHOSATE	MONSANTO		MUTAGENICITY	RAT/MOUSE	V		NO RESP
633-7507	GLYPHOSATE	MONSANTO		AMES TEST		I	NA	REPLACED
633-7801	GLYPHOSATE	MONSANTO	ASSAY	RECOMBINATION		I	NA	REPLACED
651-3917	GLYPHOSATE	MONSANTO		REPRO&RESIDUE	HEN	V		NO RESP
651-5275	GLYPHOSATE	MONSANTO		TERATOLOGY	RABBIT	I	NA	REPLACED
663-6290	GLYPHOSATE	MONSANTO	INHALATION	SUBCHRONIC	RAT	I	NA	REPLACED
8533-8920	GLYPHOSATE	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
8533-8923	GLYPHOSATE	MONSANTO		REPRODUCTION	RAT	I	NA	NO RESP
8560-8924	GLYPHOSATE	MONSANTO	FEEDING	PILOT & CHRONIC	RAT	P		NEG RESP
8580-8921	GLYPHOSATE	MONSANTO		TERATOLOGY	RABBIT	I	NA	NEG RESP
8580-8922	GLYPHOSATE	MONSANTO	ORAL	CHRONIC	DOG	P		NEG RESP
A-2468B	GLYPHOSATE	MONSANTO	DERMAL		RABBIT	I	NA	REPLACED
E-1753	GLYPHOSATE	MONSANTO			QUAIL	V	V	NEG RESP
J-3920	GLYPHOSATE	MONSANTO			SWINE	V	V	NEG RESP
632-3894	GLYPHOSATE	MONSANTO			CATTLE	V	V	NEG RESP
651-3918	GLYPHOSATE	MONSANTO			HEN	V	V	NEG RESP
8580-9117	GLYPHOSATE	MONSANTO	NEURO		HEN	V		NO RESP
A-8426	GLYPHOSINE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	NO RESP
B-330	GLYPHOSINE	MONSANTO		SUBCHRONIC	RAT	I	NA	NEG RESP
B-8424	GLYPHOSINE	MONSANTO	ORAL	SUBACUTE	RAT	S	S	NO RESP
B-9555	GLYPHOSINE	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NEG RESP
B-9558	GLYPHOSINE	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	NEG RESP
B-9560	GLYPHOSINE	MONSANTO		REPRODUCTION	RAT	P		NO RESP
C-8425	GLYPHOSINE	MONSANTO	ORAL	SUBCHRONIC	DOG	S	S	NO RESP
C-9556	GLYPHOSINE	MONSANTO	ORAL	CHRONIC	DOG	I	NA	NEG RESP
E-9561	GLYPHOSINE	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
J-9565	GLYPHOSINE	MONSANTO		TERATOLOGY	RABBIT	I	NA	NEG RESP
8580-9116	GLYPHOSINE	MONSANTO	NEURO		HEN	S	S	NO RESP
622-5557	GOODRITE 3125		ORAL	*INUTERO EXPOSURE*	RAT	V	P	NO RESP
611-5556	GOODRITE 3125		ORAL		DOG	V	P	NO RESP
8560-8881	GOSSYPLURE	CONREL	ORAL	SUBACUTE	RAT	S	S	REPLACED
8580-8883	GOSSYPLURE	CONREL	ORAL	SUBACUTE	DOG	S	S	REPLACED
611-8063	HARVADE	UNIROYAL	ORAL	SUBCHRONIC	DOG	V	NA	REPLACED
622-8070	HARVADE	UNIROYAL	ORAL	SUBCHRONIC	RAT	V	NA	REPLACED
J-6511	HEPTACHLOR EPOX	VELSICOL		REPRODUCTION	HEN	I	NA	NEG RESP
424	HINOSAN	MOBAY		MUTAGENICITY	MOUSE	I	NA	NEG RESP
C-5416	IRGASAN	CIBA GEIGY	DERMAL	SUBACUTE	DOG	I	NA	NO RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
J-7112	IRGASAN	CIBA GEIGY		REPRODUCTION	RABBIT	I	NA	NO RESP
P-7113	IRGASAN	CIBA GEIGY		REPRODUCTION	RAT	I	NA	NO RESP
622-06047	IRGASAN	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	NO RESP
A-8434	IRGASAN	CIBA GEIGY	DERMAL		RABBIT	I	NA	NO RESP
C-1435	IRGASAN	CIBA GEIGY	ORAL		DOG	I	NA	NO RESP
J-4915	IRGASAN	CIBA GEIGY	DERMAL		MOUSE	I	NA	NO RESP
602-02220	IRGASAN	CIBA GEIGY	DERMAL		MONKEY	I	NA	NO RESP
622-04554	IRGASAN	CIBA GEIGY	ORAL		RAT	I	NA	NO RESP
622-05278	IRGASAN	CIBA GEIGY	ORAL		MICE	I	NA	NO RESP
631-04784	IRGASAN	CIBA GEIGY	DERMAL		MONKEY	I	NA	REPLACED
A-6010	LASSO	MONSANTO	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-1182	LASSO	MONSANTO	ORAL	SUBCHRONIC	MOUSE	I	NA	NOT REQ
B-4477	LASSO	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	NOT REQ
B-5987	LASSO	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	NOT REQ
C-1181	LASSO	MONSANTO	ORAL	CHRONIC	DOG	I	NA	NOT REQ
C-4478	LASSO	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	NOT REQ
C-5988	LASSO	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	NOT REQ
E-1184	LASSO	MONSANTO		MUTAGENICITY	MOUSE	V	CI	NO RESP
J-1183	LASSO	MONSANTO		TERATOLOGY	RABBIT	I	NA	REPLACED
621-1180	LASSO	MONSANTO	ORAL	CHRONIC	RAT	I	NA	REPLACED
621-1182	LASSO	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	REPLACED
622-1185	LASSO	MONSANTO		REPRODUCTION	RAT	I	NA	REPLACED
8533-8849	LASSO	MONSANTO		MUTAGENICITY	MOUSE	V	CI	NO RESP
8533-8850	LASSO	MONSANTO		MUTAGENICITY	MICRORGANISM	I	NA	REPLACED
8533-8851	LASSO	MONSANTO		MUTAGENICITY	RAT	V	CI	NO RESP
8533-8852	LASSO	MONSANTO		MUTAGENICITY	MICRORGANISM	I	NA	REPLACED
663-6288	LASSO	MONSANTO	INHALATION		RAT	V		NO RESP
A-7679	MACHETE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	NOT REQ
A-7680	MACHETE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	P		NO RESP
A-9966	MACHETE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	NOT REQ
B-8703	MACHETE	MONSANTO	ORAL	SUBACUTE	RAT	I	NA	REPLACED
C-2312	MACHETE	MONSANTO	ORAL	CHRONIC	DOG	V	CM	NEG RESP
C-8704	MACHETE	MONSANTO	ORAL	SUBACUTE	DOG	S	NA	NO RESP
E-2314	MACHETE	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
621-02311	MACHETE	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	REPLACED
621-2310	MACHETE	MONSANTO	ORAL	CHRONIC	RAT	I	NA	REPLACED
622-02313	MACHETE	MONSANTO		REPRODUCTION	RAT	I	NA	REPLACED
633-8181	MACHETE	MONSANTO		RECOMBINATION	SALMONELLA	I	NA	NO RESP
651-2315	MACHETE	MONSANTO		TERATOLOGY	RABBIT	I	NA	REPLACED
8536-08181	MACHETE	MONSANTO		REVERSE MUTATION	SALMONELLA	I	NA	REPLACED
8580-9731	MACHETE	MONSANTO		REPRO & RESIDUE	HEN	V	NA	NO RESP
611-4855	MALONOBEN	GULF	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
621-8138	MALONOBEN	GULF		CARCINOGENICITY	RAT	I	NA	NEG RESP
622-4854	MALONOBEN	GULF	ORAL	SUBACUTE	RAT	I	NA	NEG RESP
651-8137	MALONOBEN	GULF		CARCINOGENICITY	MOUSE	I	NA	NEG RESP
T-1604	MBP			NEUROTOXICITY	MOUSE	I	NA	NEG RESP
E-8916	MESUROL	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
J-105	MESUROL	CHEMAGRO		DEMYLINIATION	HEN	I	NA	NEG RESP
J-2570	MESUROL	CHEMAGRO		REPRODUCTION	HEN	I	NA	NEG RESP
16063	MESUROL	CHEMAGRO	NEURO		HEN	I	NA	NEG RESP
B-8965	META SYSTOX-R	CHEMAGRO	ORAL	CHRONIC	RAT	I	NA	NO RESP
C-8966	META SYSTOX-R	CHEMAGRO	ORAL	CHRONIC	DOG	V	CI	NO RESP
J-9025	META SYSTOX-R	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	NO RESP
P-8915	META SYSTOX-R	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	NO RESP
B-7369	METHAZOLE	VELSICOL	ORAL	SUBACUTE	RAT	I	NA	NO RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
C-7370	METHAZOLE	VELSICOL	ORAL	SUBACUTE	DOG	I	NA	NO RESP
E-2097A	METHAZOLE	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
E-2097B	METHAZOLE	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
632-03373	METHAZOLE	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
8532-8239	METHAZOLE	VELSICOL	ORAL	CHRONIC	RAT	P		NEG RESP
8533-8240	METHAZOLE	VELSICOL		REPRODUCTION	RAT	S	NA	REPLACED
8580-8238	METHAZOLE	VELSICOL	ORAL	CHRONIC	MOUSE	I	NA	NEG RESP
4180	METHOMYL	DUPONT	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
A-1992	METHOPRENE	ZOECON	DERMAL	SUBACUTE	RABBIT	I	NA	NO RESP
B-1645	METHOPRENE	ZOECON	ORAL	SUBACUTE	RAT	I	NA	NO RESP
B-1982	METHOPRENE	ZOECON		TERATOLOGY	RAT	I	NA	REPLACED
J-1983	METHOPRENE	ZOECON		TERATOLOGY	RABBIT	I	NA	REPLACED
A-3773	METOBROMURON	CIBA.GEIGY	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-3972	METOBROMURON	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	NEG RESP
C-3126	METOBROMURON	CIBA GEIGY	ORAL	CHRONIC		I	NA	NO RESP
C-3769	METOBROMURON	CIBA GEIGY	ORAL	CHRONIC	DOG	I	NA	NEG RESP
P-3770	METOBROMURON	CIBA GEIGY		REPRODUCTION	RAT	I	NA	NEG RESP
3768	METOBROMURON	CIBA GEIGY	ORAL/DERMAL	SUBACUTE	RAT	I	NA	NO RESP
A-3774	METOBROMURON	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
622-7925	METOLACHLOR	CIBA GEIGY		CARCINOGENICITY	MOUSE	P		NO RESP
622-7926	METOLACHLOR	CIBA GEIGY	ORAL	CHRONIC	RAT	S	S	REPLACED
623-7928	METOLACHLOR	CIBA GEIGY		REPRODUCTION	RAT	S	S	REPLACED
A-6479	MONITOR	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-2442A	MONITOR	CHEVRON		CHOLINESTERASE	RAT	I	NA	REPLACED
B-5485	MONITOR	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-6484	MONITOR	CHEVRON		CHOLINESTERASE	RAT	I	NA	REPLACED
B-6485	MONITOR	CHEVRON		CHOLINESTERASE	DOG	I	NA	REPLACED
C-5468	MONITOR	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
C-8128	MONITOR	CHEVRON		CHOLINESTERASE	DOG	I	NA	REPLACED
E-9517	MONITOR	CHEVRON		MUTAGENICITY	MOUSE	I	NA	REPLACED
I-7081	MONITOR	CHEVRON		CHOLINESTERASE	DOG	I	NA	REPLACED
J-9515	MONITOR	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
N-9516	MONITOR	CHEVRON	INHALATION	SUBACUTE	RAT	I	NA	NEG RESP
P-6255	MONITOR	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
C-6486	MONITOR	CHEVRON	FEEDING		RAT	I	NA	REPLACED
J-6480	MONITOR	CHEVRON	NEURO		HEN	I	NA	REPLACED
J-9546	MONITOR	CHEVRON	NEURO		HEN	I	NA	REPLACED
J-8908	MORESTAN	CHEMAGRO		SPERMATOGENESIS	DOG	S	S	NEG RESP
P-8913	MORESTAN	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
651-03393	MSMA	DIAMOND SHAMROCK	DIETARY	SUBACUTE	DUCK/QUAIL	I	NA	REPLACED
B-2804	NALED	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-2948	NALED	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-3705	NALED	CHEVRON	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
C-1012	NALED	CHEVRON	ORAL	SUBACUTE	DOG	I	NA	REPLACED
C-1012	NALED	CHEVRON		DEMYELINATION	DOG	I	NA	NEG RESP
C-1240	NALED	CHEVRON	ORAL	SUBACUTE	DOG	I	NA	REPLACED
C-1446	NALED	CHEVRON	ORAL	CHRONIC	DOG	I	NA	NEG RESP
D-2203	NALED	CHEVRON	ORAL	SUBACUTE	COW	I	NA	NEG RESP
D-2203	NALED	CHEVRON		CHOLINESTERASE	RAT	I	NA	REPLACED
E-1022	NALED	CHEVRON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
OPP3	NALED	CHEVRON		NEUROTOX	CHICKEN	I	NA	NO RESP
1010	NALED	CHEVRON	ORAL	SUBACUTE	RAT	I	NA	REPLACED
1568	NALED	CHEVRON	FEEDING	SUBACUTE	RAT	I	NA	REPLACED

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
8580-8991	NALED	CHEVRON		TERATOLOGY	RABBIT	I	NA	NEG RESP
965(2-62)	NALED	CHEVRON	INHALATION	SUBACUTE	GUINEA PIG	I	NA	NEG RESP
965(7-62)	NALED	CHEVRON		PECUTANEOUS	RABBIT	I	NA	NEG RESP
B-1445	NALED	CHEVRON	ORAL		RAT	I	NA	NEG RESP
965(6-62)	NALED	CHEVRON	PATCH TEST		HUMAN	I	NA	NEG RESP
B-9068	NEMACUR	MOBAY		CARCINOGENICITY	MOUSE	I	NA	REPLACED
J-9024	NEMACUR	MOBAY		TERATOLOGY	RABBIT	I	NA	REPLACED
P-8914	NEMACUR	MOBAY		MUTAGENICITY	MOUSE	I	NA	REPLACED
621-6001	NEMEFENE	SHELL		REPRODUCTION	RAT	I	NA	NO RESP
621-6002	NEMEFENE	SHELL		REPRODUCTION	RAT	I	NA	NO RESP
623-6212	NEMEFENE	SHELL		TERATOLOGY	RAT	I	NA	NO RESP
651-6000	NEMEFENE	SHELL	ORAL	CHRONIC	DOG	I	NA	NO RESP
C-8798	NICOTINE	BLACK LEAF	ORAL		DOG	I	NA	NO RESP
J-8797	NICOTINE	BLACK LEAF			HEN	V	V	NEG RESP
J-9400	NICOTINE	BLACK LEAF			HEN	P		NO RESP
C-1772	NOREA	BFC	ORAL	CHRONIC	DOG	I	NA	NEG RESP
1771	NOREA	BFC	ORAL	CRONIC	RAT	I	NA	NEG RESP
2476	NOREA	BFC		REPRODUCTION	RAT	I	NA	NEG RESP
9/62	NOREA	BFC	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
9/62	NOREA	BFC	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
1773	NOREA	BFC	ORAL		RAT	I	NA	NEG RESP
B-1242	OMADINE	OLIN		TERATOLOGY	RAT	I	NA	NO RESP
B-346	OMADINE	OLIN		TERATOLOGY	RAT	I	NA	NO RESP
621-4599	OMADINE	OLIN	ORAL	SUBACUTE	MONKEY	I	NA	NO RESP
622-3088	OMADINE	OLIN		TERATOLOGY	RAT	I	NA	NO RESP
622-4598	OMADINE	OLIN	ORAL	SUBACUTE	RAT	I	NA	NO RESP
622-5693	OMADINE	OLIN		MUTAGENICITY	MOUSE	I	NA	NO RESP
622-8049	OMADINE	OLIN		TESTICULAR LESIO	MOUSE	P		NO RESP
623-8160	OMADINE	OLIN		TERATOLOGY	RAT	I	NA	NO RESP
623-8181	OMADINE	OLIN		MUTAGENICITY	MOUSE	I	NA	NO RESP
632-6372	OMADINE	OLIN		PLACENTAL TRANSF	RAT	I	NA	NO RESP
632-6541	OMADINE	OLIN		PLACENTAL TRANSF	PIG	I	NA	NO RESP
651-4101A	OMADINE	OLIN		TERATOLOGY	PIG	I	NA	NO RESP
651-4101B	OMADINE	OLIN		TERATOLOGY	PIG	I	NA	NO RESP
651-4101C	OMADINE	OLIN		TERATOLOGY	PIG	I	NA	NO RESP
651-4101D	OMADINE	OLIN		TERATOLOGY	PIG	I	NA	NO RESP
B-1707	OMITE-COMITE	UNIROYAL		TERATOLOGY	RAT	I	NA	REPLACED
663-4206	OMITE-COMITE	UNIROYAL	INHALATION	SUBCHRONIC	RAT	V		NO RESP
J-1201	OMITE-COMITE	UNIROYAL			HEN	V		NO RESP
651-05485	OMITE-COMITE	UNIROYAL			SWINE	V		NO RESP
A-776	ORTHENE	CHEVRON	DERMAL	SUBACUTE	BIRD	V	V	NO RESP
B-1116	ORTHENE	CHEVRON		CHOLINESTEASE	RAT	I	NA	REPLACED
B-190	ORTHENE	CHEVRON		TERATOLOGY	RAT	V	P	NO RESP
B-2442	ORTHENE	CHEVRON		CHOLINESTERASE	RAT	I	NA	REPLACED
B-8733	ORTHENE	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-8867	ORTHENE	CHEVRON	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
B-9269	ORTHENE	CHEVRON		CARCINOGENICITY	MICE	I	NA	REPLACED
B-9272	ORTHENE	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-9526	ORTHENE	CHEVRON		CHOLINESTERASE	RAT	S	S	REPLACED
C-8732	ORTHENE	CHEVRON	ORAL	CHRONIC	DOG	V	P	NO RESP
C-9527	ORTHENE	CHEVRON	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
E-193	ORTHENE	CHEVRON		MUTAGENICITY	MICE	I	NA	REPLACED
J-1378	ORTHENE	CHEVRON		REPRODUCTION	QUAIL	I	NA	NEG RESP
J-191	ORTHENE	CHEVRON		TERATOLOGY	RABBIT	I	NA	REPLACED
636-2498	ORTHENE	CHEVRON		CHOLINESTERASE	HUMAN	S	NA	NEG RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
651-4807	ORTHENE	CHEVRON		REPRODUCTION	DUCK	I	NA	REPLACED
J-2042	ORTHENE	CHEVRON			CATTLE	V	V	NO RESP
J-2493	ORTHENE	CHEVRON			PIG	V	V	NO RESP
J-513	ORTHENE	CHEVRON	NEURO		HEN	I	NA	REPLACED
A-2791	PARAQUAT	CHEVRON	INHALATION	SUBCHRONIC	RAT/PIG/DOG	I	NA	REPLACED
A-3359	PARAQUAT	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
A-3686	PARAQUAT	CHEVRON	DERMAL	SUBACUTE	RABBIT	I	NA	REPLACED
B-1350	PARAQUAT	CHEVRON	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-3796	PARAQUAT			SUBACUTE	COW	I	NA	REPLACED
C-1351	PARAQUAT	CHEVRON	ORAL	CHRONIC	DOG	I	NA	REPLACED
D-2723	PARAQUAT	CHEVRON	ORAL	SUBACUTE	COW	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	DOG	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	GUINEA PIG	I	NA	NEG RESP
D-3030	PARAQUAT	CHEVRON	INHALATION	SUBACUTE	RAT	I	NA	REPLACED
J-131	PARAQUAT	CHEVRON			DUCK	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			PHEASANT	I	NA	REPLACED
651-4020	PARAQUAT	CHEVRON	DIETARY		PHEASANT	V	P	REPLACED
651-4381	PARAQUAT	CHEVRON	DIETARY		PHEASANT	V	P	REPLACED
651-5403	PARAQUAT	CHEVRON			HEN	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			DUCK	I	NA	NEG RESP
J-131	PARAQUAT	CHEVRON			PHEASANT	I	NA	REPLACED
B-2068	PENNCAP M	PENWALT	ORAL	SUBCHRONIC	RAT	V	CI	NO RESP
J-2040	PENNCAP M	PENWALT	ORAL	SUBCHRONIC	DOG	V		NO RESP
621-4921	PENNCAP M	PENWALT	ORAT	CHRONIC	RAT	I	NA	NO RESP
A-2267	PERFLUIDONE	3M	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
8562-9315	PERFLUIDONE	3M	INHALATION	SUBACUTE	RAT	I	NA	NO RESP
A-6652	PHENMEDIPHAM	NOR AM C	DERMAL	SUBCHRONIC	RABBIT	V		NO RESP
A-7571	PHENMEDIPHAM	NOR AM C		CHOLINESTERASE	RAT	V		NO RESP
B-7149	PHENMEDIPHAM	NOR AM C	ORAL	SUBCHRONIC	RAT	V	NA	REPLACED
C-7150	PHENMEDIPHAM	NOR AM C	ORAL	SUBCHRONIC	DOG	V	NA	REPLACED
N-7657	PHENMEDIPHAM	NOR AM C	INHALATION	SUBCHRONIC	RAT	V		NO RESP
B-8882	PHENTHOATE	MONTEDISON	ORAL	CHRONIC	RAT	I	NA	NEG RESP
C-8884	PHENTHOATE	MONTEDISON	ORAL	CHRONIC	DOG	V	C	NO RESP
601-4413	PHENTHOATE	MONTEDISON	DERMAL	SUBCHRONIC	RABBIT	S	S	NEG RESP
601-4524	PHENTHOATE	MONTEDISON	DERMAL	SUBCHRONIC	RABBIT	I	NA	NEG RESP
622-4624	PHENTHOATE	MONTEDISON		ONCOGENICITY	MOUSE	I	NA	NEG RESP
622-5876	PHENTHOATE	MONTEDISON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
623-3513	PHENTHOATE	MONTEDISON		REPRODUCTION	RAT	S	S	NEG RESP
623-3803	PHENTHOATE	MONTEDISON		REPRODUCTION	RAT	S	I	NEG RESP
632-4157	PHENTHOATE	MONTEDISON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
651-5785	PHENTHOATE	MONTEDISON		TERATOLOGY	RAT	V	P	NEG RESP
651-5875	PHENTHOATE	MONTEDISON		TERATOLOGY	RABBIT	I	NA	NEG RESP
601-3892	PHENTHOATE	MONTEDISON	DERMAL		RABBIT	I	NA	NEG RESP
8580-8635	PHENTHOATE	MONTEDISON	NEURO		HEN	S	S	NEG RESP
C-1292	PHORATE	AMER CYANIMID		CHOLINESTERASE	DOG	I	NA	NO RESP
B-2804	PHOSPHAMIDON	CHEVRON		REPRODUCTION	RAT	I	NA	REPLACED
B-6960	PHOSPHAMIDON	CHEVRON						
	CHOLINESTERASE	RAT	I	NA	NEG RESP			
C-1382	PHOSPHAMIDON	CHEVRON						
ORAL	SUBACUTE	DOG	I	NA	NEG RESP			
C-1444	PHOSPHAMIDON	CHEVRON						
ORAL	CHRONIC	DOG	I	NA	REPLACED			
D-3082	PHOSPHAMIDON	CHEVRON						
	CHOLINESTERASE	RAT	I	NA	NEG RESP			

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
T-3035	PHOSPHAMIDON	CHEVRON						
INHALATION	SUBACUTE	RAT/DOG/G.P.	I	NA	NEG RESP			
WCRF 129	PHOSPHAMIDON	CHEVRON						
	DEMYELINIATION	HEN	I	NA	NO RESP			
WCRF 129R	PHOSPHAMIDON	CHEVRON						
	DEMYELINIATION	HEN	I	NA	NEG RESP			
1002A	PHOSPHAMIDON	CHEVRON						
	DEMYELINIATION	DOG	I	NA	NEG RESP			
1002B	PHOSPHAMIDON	CHEVRON						
	CHOLINESTERASE	DOG	I	NA	NEG RESP			
2589	PHOSPHAMIDON	CHEVRON						
	COMPARATIVE		I	NA	NEG RESP			
A-3085	PHOSPHAMIDON	CHEVRON						
ORAL		RAT	I	NA	REPLACED			
B-1443	PHOSPHAMIDON	CHEVRON						
ORAL		RAT	I	NA	NEG RESP			
B-8799	PICLORAM	DOW		TERATOLOGY	MOUSE	I	NA	REPLACED
C-1975	PICLORAM	DOW	ORAL	CHRONIC	DOG	I	NA	REPLACED
1974	PICLORAM	DOW	ORAL	CHRONIC	RAT	I	NA	REPLACED
2198	PICLORAM	DOW	PATCH TEST		HUMAN	I	NA	REPLACED
601-5447	PIK OFF	CIBA GEIGY	DERMAL	SUBACUTE	RABBIT	S	CS	NEG RESP
611-5277	PIK OFF	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
611-6090	PIK OFF	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
622-5276	PIK OFF	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
8533-9374	PIK OFF	CIBA GEIGY	ORAL	CHRONIC	RAT	S	CS	NEG RESP
8533-9375	PIK OFF	CIBA GEIGY		REPRODUCTION	RAT	V	CM	NEG RESP
8533-9743	PIK OFF	CIBA GEIGY		TERATOLOGY	RAT	I	NA	NEG RESP
8536-10509	PIK OFF	CIBA GEIGY		MUTAGENICITY	SALMONELLA	I	NA	NEG RESP
8580-9376	PIK OFF	CIBA GEIGY		CARCINOGENICITY	MOUSE	I	NA	NEG RESP
8533-08317	PIPERONYL BUTOX	MGK		TERATOLOGY	RAT	I	NA	NOT REQ
663-6080	PIPERONYL BUTOX	MGK	INHALATION		MOUSE	V		NO RESP
B-1714	POLYRAM	FMC	ORAL	SUBACUTE	RAT	I	NA	REPLACED
B-1715	POLYRAM	FMC	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-1715A	POLYRAM	FMC	ORAL	CHRONIC	RAT	I	NA	REPLACED
B-2705	POLYRAM	FMC		REPRODUCTION	RAT	I	NA	REPLACED
B-2766	POLYRAM	FMC	ORAL	SUBACUTE	RAT	I	NA	REPLACED
C-1716	POLYRAM	FMC	ORAL	CHRONIC	DOG	I	NA	NOT REQ
2178	POLYRAM	FMC	PERCUTAN	SUBACUTE	RABBIT	I	NA	NO RESP
2790	POLYRAM	FMC	ORAL	SUBACUTE	DOG	S	CS	NO RESP
B-5366	POTASSIUM AZIDE	PPG	ORAL	SUBACUTE	RAT	I	NA	NOT REQ
C-5367	POTASSIUM AZIDE	PPG	ORAL	SUBACUTE	DOG	I	NA	NOT REQ
622-3539	POTASSIUM AZIDE	PPG		TERATOLOGY	RAT	I	NA	NOT REQ
B-6758	POTASSIUM HEXA	PENWALT	ORAL	SUBACUTE	RAT	I	NA	NOT REQ
C-6759	POTASSIUM HEXA	PENWALT	ORAL	SUBCHRONIC	DOG	I	NA	NOT REQ
C-7380	POTASSIUM HEXA	PENWALT	THYROID	FUNCTION	DOG	I	NA	NOT REQ
B-8262	PPG 124	PPG	ORAL	SUBCHRONIC	DOG	I	NA	NO RESP
C-8262	PPG 124	PPG	ORAL	SUBACUTE TOX	DOG	I	NA	NEG RESP
B-8829	PRODIAMINE	VELSICOL		SUBCHRONIC	RAT	I	NA	NO RESP
E-399	PRODIAMINE	VELSICOL		MUTAGENICITY	MOUSE	I	NA	NO RESP
601-6055	PRODIAMINE	VELSICOL	DERMAL	SUBACUTE	RABBIT	I	NA	NO RESP
621-6644	PRODIAMINE	VELSICOL	ORAL	CHRONIC	RAT	S	CS	NO RESP
623-6981	PRODIAMINE	VELSICOL		REPRODUCTION	RAT	I	NA	NO RE...

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
651-6116	PRODIAMINE	VELSICOL		TERATOLOGY	RABBIT	I	NA	NO RESP
651-6224	PRODIAMINE	VELSICOL	ORAL	SUBCHRONIC	DOG	I	NA	NO RESP
651-6643	PRODIAMINE	VELSICOL		CATARACTEGEN	HEN	I	NA	NO RESP
651-7145	PRODIAMINE	VELSICOL		CARCINOGENICITY	MOUSE	I	NA	NO RESP
B-904	PROFLURALIN	CIBA GEIGY		TERATOLOGY	RAT	V	NA	NOT REQ
C-476	PROFLURALIN	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	V		NEG RESP
P-475	PROFLURALIN	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	V	NA	NEG RESP
A-675	PROFLURALIN	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
B-904	PROMETON	CIBA GEIGY		TERATOLOGY	RAT	S	P	NO RESP
	PROMETRYN	FMC	DERMAL		RABBIT	I	NA	NEG RESP
B-5633	PROPHAM	PPG	ORAL	SUBACUTE	RAT	I	NA	REPLACED
C-5634	PROPHAM	PPG	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
J-8630B	PROPHAM	PPG			HEN	V	V	NEG RESP
B-1374A	PROWL	AMER CYANIMID		TERATOLOGY	RAT	I	NA	REPLACED
B-2324	PROWL	AMER CYANIMID		TERATOLOGY	RAT	I	NA	REPLACED
8580-9771	PROWL	AMER CYANIMID		CATARACTEGEN	HEN	V	CM	NEG RESP
663-6080	PYRETHRIN	MGK	INHALATION		MOUSE	V	P	NO RESP
J-239	RABON	SHELL		TERATOLOGY	RABBIT	I	NA	REPLACED
A-1330	RAMROD	MONSANTO	DERMAL	SUBACUTE	RABBIT	I	NA	NOT REQ
A-7183	RAMROD	MONSANTO	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
B-1174	RAMROD	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	NEG RESP
B-5063	RAMROD	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NOT REQ
B-5064	RAMROD	MONSANTO	ORAL	CHRONIC	DOG	I	NA	NOT REQ
B-5065	RAMROD	MONSANTO		REPRODUCTION	RAT	I	NA	NOT REQ
B-5083	RAMROD	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	NOT REQ
B-5084	RAMROD	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	NOT REQ
C-1173	RAMROD	MONSANTO	ORAL	CHRONIC	DOG	I	NA	
E-1177	RAMROD	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
J-1175	RAMROD	MONSANTO		TERATOLOGY	RABBIT	I	NA	NEG RESP
621-1172	RAMROD	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NEG RESP
622-1176	RAMROD	MONSANTO		REPRODUCTION	RAT	I	NA	NEG RESP
663-6289	RAMROD	MONSANTO	INHALATION	SUBACUTE	RAT	I	NA	NEG RESP
E-1751	RAMROD	MONSANTO			QUAIL	V	V	NEG RESP
J-7214	RAMROD	MONSANTO	DIETARY		QUAIL	I	NA	NOT REQ
621-1174	RAMROD	MONSANTO	ORAL		MOUSE	I	NA	REPLACED
B-4806	RANDOX	MONSANTO	ORAL	SUBACUTE	RAT	I	NA	NEG RESP
C-4807	RANDOX	MONSANTO	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
621-06952	RANDOX	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NEG RESP
623-6953	RANDOX	MONSANTO		REPRODUCTION	RAT	I	NA	NEG RESP
623-7090	RANDOX	MONSANTO		MUTAGENICITY	MOUSE	V	CI	NO RESP
651-0791	RANDOX	MONSANTO		TERATOLOGY	RABBIT	I	NA	NEG RESP
B-5580	RESMETHRIN		ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
J-5579	RESMETHRIN			TERATOLOGY	RABBIT	I	NA	REPLACED
J-6146	RESMETHRIN			TERATOLOGY	RABBIT	I	NA	REPLACED
P-6178	RESMETHRIN			TERATOLOGY	MOUSE	I	NA	REPLACED
	RONNEL	DOW	TISS/SKEL	TERATOLOGY	RAT	I	NA	NEG RESP
A-2007	SANTOPHEN	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	NO RESP
B-2010	SANTOPHEN	MONSANTO	ORAL	SUBCHRONIC	RAT	S	S	NO RESP
C-2009	SANTOPHEN	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	NO RESP
C-2011	SANTOPHEN	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	NO RESP
E-2014	SANTOPHEN	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NO RESP
J-2013	SANTOPHEN	MONSANTO		TERATOLOGY	RABBIT	I	NA	NO RESP
M-2041	SANTOPHEN	MONSANTO	INHALATION	SUBACUTE	RAT	I	NA	NO RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
622-2012B	SANTOPHEN	MONSANTO		REPRODUCTION	RAT	P		NO RESP
622-2012C	SANTOPHEN	MONSANTO		TERATOLOGY	RAT	I	NA	NO RESP
8562-8408	SECTROL	3M	INAHLATION		RAT	I	NA	REPLACED
B-9069	SENCOR	CHEMAGRO		CARCINOGENICITY	MOUSE	I	NA	REPLACED
C-7760	SENCOR	CHEMAGRO	ORAL	SUBACUTE	DOG	V	P	NO RESP
E-8922	SENCOR	CHEMAGRO		MUTAGENICITY	MOUSE	I	NA	REPLACED
J-1851	SENCOR	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	REPLACED
J-233	SENCOR	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	REPLACED
J-9027	SENCOR	CHEMAGRO		TERATOLOGY	RABBIT	I	NA	REPLACED
B-9071	SIMAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
B-9244	SIMAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	NOT REQ
8532-8869	SIMAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	MOUSE	I	NA	NEG RESP
8580-8907	SIMAZINE	CIBA GEIGY		CARCINOGENICITY	MOUSE	I	NA	DISCUSSION
622-3540	SODIUM AZIDE	PPG		TERATOLOGY	RAT	I	NA	NOT REQ
B-5664	SODIUM CHLORATE		ORAL		RAT	I	NA	NEG RESP
C-5665	SODIUM CHLORATE		ORAL		DOG	I	NA	NEG RESP
B-904	SUMITOL	CIBA GEIGY		TERATOLOGY	RAT	V	NA	NO RESP
8580-9380	SUPRACIDE	CIBA GEIGY	ORAL	CHRONIC	MOUSE	S	P	REPLACED
A-7198	SUPRACIDE	CIBA GEIGY	DERMAL		RABBIT	V	NA	REPLACED
2705	TEDION	FMC		REPRODUCTION	RAT	I	NA	NEG RESP
B-13748	TERBUFOS	AMER CYANIMID		TERATOLOGY	RAT	I	NA	NO RESP
A-904	TERBUTHYLAZINE	CIBA GEIGY		TERATOLOGY	RAT	V		NEG RESP
B-3797	TERBUTHYLAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
B-4538	TERBUTHYLAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP
B-8210	TERBUTHYLAZINE	CIBA GEIGY	ORAL	CHRONIC	RAT	P		NEG RESP
B-8211	TERBUTHYLAZINE	CIBA GEIGY	ORAL	CHRONIC	RAT	I	NA	NEG RESP
C-8270	TERBUTHYLAZINE	CIBA GEIGY	ORAL	SUBCHRONIC	DOG	I	NA	NEG RESP
C-8271	TERBUTHYLAZINE	CIBA GEIGY	ORAL	CHRONIC	DOG	I	NA	NEG RESP
P-8272	TERBUTHYLAZINE	CIBA GEIGY		REPRODUCTION	RAT	P		NEG RESP
A-8750	TERBUTHYLAZINE	CIBA GEIGY	DERMAL		RABBIT	P		NEG RESP
N-8750	TERBUTHYLAZINE	CIBA GEIGY	DERMAL		RABBIT	I	NA	NEG RESP
B-904	TERBUTRYN	CIBA GEIGY		TERATOLOGY	RAT	V		REPLACED
A-5456	TERBUTRYN	CIBA GEIGY	DERMAL		RABBIT	I	NA	NOT REQ
B-3799	TERBUTRYN	CIBA GEIGY	ORAL		RAT	I	NA	REPLACED
J-5286	TERBUTRYN	CIBA GEIGY	ORAL		DOG	I	NA	REPLACED
8533-10590	TERRAZOLE	OLIN		TERATOLOGY	RAT	S	S	REPLACED
8531-8338	THIDIAZURON	NORAM	ORAL	SUBCHRONIC	DOG	S	CS	REPLACED
8533-9630	THIDIAZURON	NORAM		REPRODUCTION	RAT	V	C	NEG RESP
8560-8337	THIDIAZURON	NORAM	ORAL	SUBCHRONIC	RAT	S	CS	NOT REQ
8560-9361	THIDIAZURON	NORAM	ORAL	CHRONIC	RAT	S	S	REPLACED
8580-10725	THIDIAZURON	NORAM		ONCOGENICITY	MOUSE	V	C	NEG RESP
B-1056	THIODAN	FMC		TERATOLOGY	RAT	I	NA	REPLACED
B-2661	THIODAN	FMC	ORAL	SUBACUTE	RAT	I	NA	REPLACED
C-2665	THIODAN	FMC	ORAL	SUBACUTE	DOG	I	NA	REPLACED
C-3758	THIODAN	FMC	ORAL	CHRONIC	DOG	V	P	NO RESP
C-8705	THIODAN	FMC	ORAL	CHRONIC	DOG	V	P	NOT REQ
E-10578	THIODAN	FMC		MUTAGENICITY	MOUSE	V	CI	REPLACED
2705	THIODAN	FMC		REPRODUCTION	RAT	I	NA	REPLACED
J-4885	THIODAN	FMC			HEN	V	V	NEG RESP
B-1390	THIOFANOX	DIAMOND SHAMROCK	ORAL	SUBCHRONIC	RAT	I	NA	NO RESP
651-6885	THIOFANOX	DIAMOND SHAMROCK		NEUROTOX	CHICKEN	V	P	NO RESP
651-7054	THIOFANOX	DIAMOND SHAMROCK		NEUROTOX	CHICKEN	V	P	NOT REQ
B-4008	TORAK	BFC	ORAL	SUBACUTE	RAT	I	NA	NEG RESP
B-4055	TORAK	BFC	ORAL	SUBCHRONIC	RAT	I	NA	NEG RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
B-4056	TORAK	BFC		CHOLINESTERASE	RAT	S	S	NEG RESP
B-4345	TORAK	BFC	ORAL	CHRONIC	RAT	I	NA	NEG RESP
C-4007	TORAK	BFC	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
C-4350	TORAK	BFC	ORAL	CHRONIC	DOG	I	NA	NEG RESP
E-4009	TORAK	BFC		CHOLINESTERASE	RAT	I	NA	NEG RESP
F-7110	TORAK	BFC		CHOLINESTERASE	HUMAN	I	NA	NEG RESP
F-7493	TORAK	BFC		CHOLINESTERASE	HUMAN	I	NA	NEG RESP
J-4529	TORAK	BFC		TERATOLOGY	RABBIT	I	NA	NEG RESP
M-6336	TORAK	BFC		CHOLINEST&TERATO	MONKEY	I	NA	NEG RESP
M-7310	TORAK	BFC		REPRODUCTION		I	NA	NEG RESP
P-4347	TORAK	BFC		REPRODUCTION	RAT	I	NA	NEG RESP
WCRF 158	TORAK	BFC		TERATOLOGY	RABBIT	I	NA	NEG RESP
623-3751	TORAK	BFC		REPRO & TERATOLO	RAT	P		NEG RESP
A-7308	TORAK	BFC	DERMAL		RABBIT	I	NA	NEG RESP
A-7848	TORAK	BFC	DERMAL		RABBIT	S	NA	NEG RESP
J-6351	TORAK	BFC	NEURO		HEN	I	NA	NEG RESP
2330	TOXAPHENE	BFC	ORAL	CHRONIC	DOG	I	NA	NEG RESP
2367	TOXAPHENE	BFC	INHALATION	SUBACUTE	DOG	I	NA	NEG RESP
2367	TOXAPHENE	BFC	INHALATION	SUBACUTE	RAT	I	NA	NEG RESP
2367	TOXAPHENE	BFC	INHALATION	SUBACUTE	GUINEA PIG	I	NA	NEG RESP
2476	TOXAPHENE	HERCULES		REPRODUCTION	RAT	I	NA	NO RESP
632-6451	TOXAPHENE	BFC	ORAL		HEN	V	NA	NEG RESP
A-8149	TRIALLATE	MONSANTO	DERMAL	SUBCHRONIC	RABBIT	I	NA	REPLACED
B-4834	TRIALLATE	MONSANTO	ORAL	SUBCHRONIC	RAT	I	NA	REPLACED
C-4835	TRIALLATE	MONSANTO	ORAL	SUBCHRONIC	DOG	I	NA	REPLACED
622-5251	TRIALLATE	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NEG RESP
622-5253	TRIALLATE	MONSANTO		MUTAGENICITY	MOUSE	V	P	NO RESP
623-6842	TRIALLATE	MONSANTO		REPRODUCTION	RAT	V	P	NO RESP
651-5255	TRIALLATE	MONSANTO		TERATOLOGY	RABBIT	I	NA	REPLACED
8530-9030	TRIALLATE	MONSANTO		CHOLINESTERASE	RAT	V	P	NO RESP
8580-10581	TRIALLATE	MONSANTO	ORAL	CHRONIC	DOG	V	P	NO RESP
A-6678	TRIALLATE	MONSANTO			FISH	I	NA	REPLACED
A-6679	TRIALLATE	MONSANTO			FISH	I	NA	REPLACED
J-6676	TRIALLATE	MONSANTO			QUAIL	I	NA	REPLACED
J-6677	TRIALLATE	MONSANTO			QUAIL	I	NA	NOT REQ
651-2842	TRIALLATE	MONSANTO	ORAL		DUCK	V	P	NO RESP
651-3023	TRIALLATE	MONSANTO	ORAL		QUAIL	V	P	NO RESP
8532-10763	TRIALLATE	MONSANTO	ORAL		MOUSE	I	NA	NEG RESP
8580-10814	TRIALLATE	MONSANTO	NEURO		HEN	I	NA	NEG RESP
8580-9120	TRIALLATE	MONSANTO	NEURO		HEN	V		NO RESP
622-5459	TRIFORINE	CHEVRON		MUTAGENICITY	MOUSE	I	NA	NEG RESP
663-5460	TRIFORINE	CHEVRON	INHALATION	SUBACUTE	RAT	I	NA	NEG RESP
B-4634	TRIPHENYLTIN HYD	THOMPSON-HAYWARD	ORAL	SUBACUTE	RAT	I	NA	NOT REQ
C-3964	TRIPHENYLTIN HYD	THOMPSON-HAYWARD	ORAL	SUBACUTE	DOG	I	NA	NOT REQ
C-4343	TRIPHENYLTIN HYD	THOMPSON-HAYWARD	ORAL	SUBACUTE	DOG	I	NA	NOT REQ
611-8069	TRIVAX	UNIROYAL	ORAL		DOG	V	NA	NEG RESP
8532-8071	TRIVAX	UNIROYAL	ORAL		RAT	V	NA	NEG RESP
I7721	VAPONA	SHELL		CHOLINESTERASE	DOG	I	NA	NEG RESP
1568	VAPONA	SHELL	ORAL	SUBACUTE	RAT	I	NA	NEG RESP
C-4805	VEGADEX	MONSANTO	ORAL	SUBACUTE	DOG	I	NA	NEG RESP
621-6954	VEGADEX	MONSANTO	ORAL	CHRONIC	RAT	I	NA	NEG RESP
623-6955	VEGADEX	MONSANTO		REPRODUCTION	RAT	I	NA	NEG RESP
623-7092	VEGADEX	MONSANTO		MUTAGENICITY	MOUSE	I	NA	NEG RESP
651-7093	VEGADEX	MONSANTO		TERATOLOGY	RAT	I	NA	NEG RESP

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
8530-9030	VEGADEX	MONSANTO		CHOLINESTERASE	RAT	V	NA	NO RESP
8532-10764	VEGADEX	MONSANTO	ORAL	SUBCHRONIC	MOUSE	I	NA	NEG RESP
8580-10582	VEGADEX	MONSANTO	ORAL	CHRONIC	DOG	I	NA	NEG RESP
B-4804	VEGADEX	MONSANTO	ORAL		RAT	I	NA	REPLACED
8580-10815	VEGADEX	MONSANTO	NEURO		HEN	V		NO RESP
8580-9118	VEGADEX	MONSANTO	NEURO		HEN	I	NA	NEG RESP
651-6763	VEL	SANDOZ	NUERO		HEN	I	NA	NO RESP
A-1159	VENDEX	SHELL	DERMAL	SUBACUTE	RABBIT	I	NA	NEG RESP
8560-8838	VINYZENE	VENTRON	ORAL	SUBACUTE	RAT	I	NA	DISCUSSION
622-07392	VORLEX		ORAL	SUBCHRONIC	RAT	V	P	NO RESP
623-07393	VORLEX			REPRODUCTION	RAT	V	P	NO RESP
	2,4-D	DOW	DERMAL	SUBACUTE	RABBIT	I	NA	NO RESP
	4-AMINOPYRIDINE	AVITROL CORP		SUBACUTE	DOG/SWINE	I	NA	NO RESP

EXHIBIT 7

9/4/84

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor (PM#25)
Registration Division (TS-767C)

THRU: Christine F. Chaisson, Ph.D.
Head, Review Section No. 4
Toxicology Branch
Hazard Evaluation Division (TS-769C)

FROM: William Dykstra, Ph.D. WHD 9/4/84
Toxicology Branch
Hazard Evaluation Division (TS-769C)

SUBJECT: Glyphosate; EPA Reg.#: 524-308; mouse oncogenicity study.
Caswell #: 661A Accession #: 251007-014

Recommendations:

1. Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The study is acceptable as core-minimum data.

2. A risk assessment by Toxicology Branch is required.

Review:

1. A chronic feeding study of Glyphosate in mice (Biodynamics # BDN-77-420; Project No. 77-2061; 7/21/83)

Test Material:

Glyphosate technical, purity = 99.7%; fine, white clumped powder; lot number, NB178260813; NB178261017.

Groups of 50 male and 50 female randomized CD-1 mice, individually caged, were administered diets containing 0, 1000, 5000, and 30,000 ppm of test material for 24 months.

Parameters evaluated were toxic signs, mortality, body weight, food consumption, water consumption and hematology at 12, 18 and 24 months.

All animals were necropsied and selected organs were weighed. Tissues were stained in H and E and examined microscopically.

Statistical analyses of the data were performed

Results:

No treatment-related toxic signs were noted during the study. Mortality was low during the first 18 months of the study as shown in the table below taken from the report:

Cumulative Mortality

DOSE	Males			Females		
(ppm)	12 Mo	18 Mo	24 Mo	12 Mo	18 Mo	24 Mo
0	9	12	30	3	15	30
1,000	9	19	34	4	16	38
5,000	7	14	33	1	8	23
30,000	4	11	24	5	13	27

Body weight was consistently decreased for males and to a lesser extent, females at the 30,000 ppm dosage level during the study at several sampling intervals. Changes in body weight at the low- and mid-dose groups were variable and not dose-related.

Food consumption showed no compound-related or dose-related effect. Hematological values although significant in some instances did not show a consistent dose-related response.

Necropsy did not show treatment-related lesions. There was good correlation between gross and microscopic findings. The relative and absolute weight of the testes and ovaries were increased in high dose males and females, but no histopathological finding was presnt as a underlying factor.

Renal tubule adenomas occurred in male mice in the following manner as taken from the report:

Dose (ppm)	0	1,000	5,000	30,000
Number examined	49	49	50	50
Renal tubule adenoma	0	0	1	3

They occurred in male mice 4029, 4032 and 4041 of the high-dose, and male 3023 of the mid-dose group.

These tumors are rare, dose related and considered compound-related. These tumors were present at terminal kill.

Other neoplasmas were considered unrelated to treatment. No effect on latency was noted.

Significant trends and significant high-dose effects were observed in non-neoplastic lesions. The lesions considered treatment-related were hepatocyte hypertrophy, central lobular hepatocyte necrosis and chronic interstitial nephritis in high-dose males and proximal tubule epithelial basophilia and hypertrophy in high-dose females.

The table below taken from the report shows the incidence of these lesions:

	Control	Low	Mid	High	Linear Trend
Central lobular hepatocyte hypertrophy					
- males	9/49	5/50	3/50	17/50	b
- females	3/49	5/50	1/49	1/49	
Central lobular hepatocyte necrosis					
- males	0/49	2/50	2/50	10/50[a]	b
- females	2/49	1/50	4/49	2/49	
Chronic interstitial nephritis					
- males	5/49	2/49	7/50	12/50	b
- females	4/50	8/50	2/50	4/50	
Proximal tubule epithelial basophilia and hypertrophy					
- males	15/49	10/49	15/50	7/50	
- females	0/50	2/50	4/50	9/50[a]	b

---

[a] Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-Square test (uncorrected for continuity).

[b] Statistically significant linear trend ($p \leq 0.01$) using the Cochran-Armitage test.

Conclusion:

Glyphosate was oncogenic in male mice producing a dose-related increase in renal tubule adenomas, a rare tumor. Dose-related non-neoplastic lesions occurred in both sexes. NO NOEL for systemic effects was established because of the dose-response relationship of proximal tubule epithelial basophilia and hypertrophy in females.

Classification:

Core minimum data.

EXHIBIT 8

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

MAR 4 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Consensus Review of Glyphosate
Caswell No. 661A

TO: Robert Taylor
Product Manager
Herbicide - Fungicide Branch
Registration Division

On February 11, 1985, a group of Toxicology Branch personnel met to evaluate and discuss the data base on Glyphosate, and in particular the potential oncogenic response of Glyphosate.

A. The following persons were in attendance:

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch

Louis Kasza, D.V.M., Ph.D.
Pathologist

Bertram Litt, Statistician

Herbert Lacayo, Ph.D.
Statistician

Reto Engler, Ph.D.

William Dykstra, Ph.D.
Reviewer

Steve Saunders, Ph.D.

Laurence Chitlik, D.A.B.T.

The signatures above indicate concurrence with this concensus report.

B. The material available for review consisted of a package issued on January 25, 1985 (attached) and a letter from Monsanto (dated February 5, 1985), rebutting the significance of renal mouse tumors.

C. Evaluation of the Facts:

1. Long-term/Pivotal Studies:

a) A 26-month rat study showed a NOEL at 30 mg/kg/day which was the HDT. The oncogenic potential at this level was negative, corroborated by an outside consultant. Although some thyroid tumors were observed in female rats in this study they were generally discounted in their significance, in and of themselves. However, it should be noted that on a mg/kg/day basis the exposure of rats was less than 1/100 of the exposure of mice (4,500 mg/kg/day). Since a toxic, or MTD, level was not reached in this study, the panel raised the conjectural issue that at toxic levels at or close to a MTD, tumors might have been induced.

b) The NOEL in a rat 3-generation reproduction study was 10 mg/kg/day. In separate teratogenicity studies feto toxic effects were noted in rats and rabbits at levels which caused significant maternal toxicity, including death; terata were not observed (ibid). These results were, however, not entered into the discussion on Glyphosate.

2. Mutagenicity Assays:

Glyphosate was tested for mutagenic activity (1) Reverse Mutation in S. typhimurium. and E. coli with and without microsomal activation, (2) Ames Assay with and without activation, (3) CHO cells with and without activation, (4) DNA repair in rat hepatocytes, (5) Rec-assay in B subtilis, and (6) Dominant lethal assay in mice. All these tests were negative, tests 1-3 are fairly well predictive of oncogenic response while 4-6 are less appropriate. An in vivo bone marrow cytogenetics study was also performed. It was negative, but scientifically not acceptable. In summary, several appropriate and scientifically acceptable tests are supportive of non-oncogenic potential of Glyphosate.

3. In the chronic mouse study carried out by Biodynamics (#BDN-77-420) renal tubule adenomas were observed in males.

Dose (ppm)	0	1000	5000	30,000
No. Exposed	49	49	50	50
Tumors	0	0	1	3

See review of W. Dykstra (dated 9/4/84).

This is a rare tumor even in Charles River CD-1 male mice. Biodynamics historical data (included in package) show that this tumor was observed only 3 times in 14 male control groups ranging in size between 51 and 60 mice.

The probability of observing this tumor 4 times or more in 198 mice (the total number of mice examined in the Glyphosate study) is p = 0.0064 when considering the historical control of the same laboratory. Even considering other reported historical controls, the p-value is low, about 0.01 indicating that it is very unlikely that the glyphosate test group is consistent with any historical controls. (See review by Dr. Lacayo).

In addition, the response rate (see above) seems to be related to the dose.

Therefore, it was the concensus of the group that the renal tubular adenomas were related to compound administration, since their frequency was not consistent with the historical controls and there is a trend indicating dose dependency.

3a. The group noted that there were other non-oncogenic, i.e., toxicological changes apparant in the kidney and liver e.g., central lobular hepatocyte hypertrophy and necrosis and chronic interstitial nephritis in males and proximal tubule epithelial basophylia and hypertrophy in females. The group discussed the possibility of kidney irritation and formulation of crystals but noted that kidney or bladder precipitaters were not reported for this assay. Therefore, a conclusion mitigating the renal tumors could not be reached.. (See page 10 of contractor review).

D. Other Considerations:

The review panel recognizes that the exposure of mice was at a very high level 4.5 g/kg/day. Precipitation of Glyphosate in the kidneys might have occurred but none was reported. The panel believes that additional sectioning of new blocks of male kidneys might help in the interpretation of the study results. The kidney tumors as reported, were unilateral (pers. communication by Dr. Dykstra, after the panel meeting); additional histopathology could resolve the issue of whether this is a valid observation or due to not "finding" the tumors in the particular block analyzed.

The panel also believes that realistic exposure assessment, both for dietary and worker exposure are of singular importance. For example, the limit of detecting residue tolerances may overestimate exposure. Particular emphasis also should be given to residues in water, since Glyphosate has been used for aquatic weed control (EUP) and this use may become the subject of a permanent registration.

E. Classification of Glyphosate:

In accordance with EPA proposed guidelines (FR of Nov. 23, 1984) the panel has classified Glyphosate as a Category C oncogen.

ADDENDUM:

The letter by Monsanto (Feb. 4, 1985) has been considered in these deliberations. Several of the issues raised are, in fact, addressed in the above deliberations, although not point by point. A point by point rebuttal, including those points with little merit, will be done in addition to this evaluation.

Attachments

cc: B. Coberly
Caswell No. 661A

EXHIBIT 9

6/14/85

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

JUN 14 1985

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Analysis of Glyphosate. Caswell No. 661A

FROM: Reto Engler, Ph.D.
Chief, Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Robert Taylor, Product Manager #25
Herbicide/Fungicide Branch
Registration Division (TS-767)

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Though a peer review of the evidence of oncogenicity of Glyphosate (memo of March 4, 1985) we have determined that the incidence of renal adenomas in male mice (a rare tumor) is inconsistent with the historical control incidence of this tumor. The registrant, in several letters, has refuted our statistical analysis of the data. Basically the registrant contends that the highest incidence ever observed in historical controls should be used to judge the incidence in the Glyphosate study. The use of any historical control data in this manner is biologically as well as statistically inappropriate and misleading.

The registrant has now submitted a report which shows that a re-reading of the kidney slides has revealed one (1) kidney tumor in the control group but no additional tumors in the treatment groups. We are in the process of analyzing the data, given this new information. However, this raises some new concern with regard to the histopathological examination of the male mouse kidneys. In fact the peer review panel offered the suggestion to systematically and uniformly recut the kidneys to obtain further information on the presence or absence of these kidney tumors. Given the overall uncertainty concerning the significance of the observed tumor incidence we believe that such a systematic reevaluation of this kidney lesion has become necessary in order to fully evaluate Glyphosate.

cc: S. Saunders
W. Burnam
A. Barton

EXHIBIT 10

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

FEB 26 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Use of historical data in determining the weight of evidence from kidney tumor incidence in the Glyphosate two-year feeding study; and some remarks on false positives

TO: Reto Engler, Chief
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

FROM: Herbert Lacayo, Statistician
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

Herbert Lacayo 2/26/85

THRU: Bertram Litt, Statistics Team Leader
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

3/4/85

BACKGROUND

The Glyphosate feeding study (EPA Reg. #: 524-308, Caswell #: 661A, Accession #: 251007-014) on Charles River CD-1 mice generated renal tubular adenomas in male mice at the 5000 and 30000 ppm dose levels. The registrant (Monsanto) claims that such tumors are "unrelated to treatment." (ref.1). In support of that they provide historical data from Bio/dynamics and two other laboratories (ref.2).

With respect to historical data we note the large number and variety of factors which influence the life history of rodents in chronic studies. Hence, it is generally agreed that the most relevant historical controls are experiments from the subject laboratory studied within a 3 to 4 year "window" (ref.3).

SUMMARY

The main purpose of this memo is to show one way historical data may be used to evaluate the significance of tumors in the glyphosate feeding study. When these data are so used we can conclude that Glyphosate dosing has a statistically significant effect (at the p = .006 level) in the production of kidney tumors in male mice. The appropriate procedure is outlined in the next section entitled Use of Historical Data. The last Section, Remarks on False Positives, addresses some comments by Monsanto (Ref.1) on this subject. That section outlines some of the weaknesses in Monsanto's position.

USE OF HISTORICAL DATA

The following information was derived from Reference 2.

Data Source*	p (est.of tumor rate)	Sigma (est.of standard deviation)
Bio/dynamics	.00368	.00212
IRD Corp.	.00437	.00109
Combined	.00399	.00094

The value p = .00368, derived from Bio/dynamics data is a reasonable choice to use as a historical control. The data are from the same laboratory that performed the Glyphosate study and are within the appropriate 3-4 year time "window" (ref.3). Further, the standard deviation of the estimate is reasonably small.

We will now examine the Monsanto contention that the kidney tumors are unrelated to treatment. (i.e. Glyphosate has no effect on kidney tumors). First, consider the tumor rate in the Glyphosate Study: 4/198 = .0202 ---

In contrast, Bio/dynamics has the lower historical rate:

3/815 = .00368

The relevant question is: What is the probability that the 198 CD-1 mice in the Glyphosate study will produce by pure chance 4 or more mice with kidney tumors? Another way of stating this is - How likely are we to have a tumor rate of .0202 --- for the Glyphosate study given that the historical rata is .00368?

Questions of this type may be answered from manipulation of the relevant distribution which, in this case is the Binomial:

$$P(r \text{ out of } n \text{ mice have tumors}) = \binom{n}{r} p^r q^{n-r}$$

Where: n = the # of male mice in the study

r = the # of male mice with kidney tumors

p = .00368, the historical probability that an individual male mouse will develop kidney tumors.

q = 1 - p

*This does not include Hazleton Laboratories America, Inc. due to the small sample size of that data set

Using the above distribution and elementary but tedious calculations, we generate the following table:

# of mice with tumor	Probability that r or more mice will have tumors in a study with 198 male mice
r = 0	1.
1	.518177
2	.165711
3	.037443
4	.006481

This last table indicates that based on a historical rate of p= .00368 that the probability of seeing 3 or more mice with kidney tumors is about .037; and the probability of seeing 4 or more such mice (i.e. seeing what in fact happened) is about .0064. We note that even considering data from I.R.D., the p value is about .01.

Under such circumstances a prudent person would reject the Monsanto assumption that Glyphosate dosing has no effect on kidney tumor production. Another way of saying this is that if Glyphosate were truly unrelated to kidney production we would expect to see 4 or more tumors in less than 1 out of 100 experiments of the type sponsored by Monsanto. Thus, Glyphosate is suspect.

REMARKS ON FALSE POSITIVES

In ref. 1 Monsanto notes that "...if 20 types of lesions were evaluated at a probability level of .05, the number expected to be positive would not be one in 20, but rather the probability would be 64 in 100, an unacceptably high value..." Monsanto is referring to the well-known fact that by examining enough data it is likely that one will find an excess of some tumor type by chance alone; thus generating a false positive.

The Monsanto argument required the following assumptions:

1. A mouse may develop 20 distinct and independent (in the statistical sense) types of tumors.
2. The probability of each tumor type in a typical mouse is .05.

It follows from the above that:

$$P(\text{a mouse has at least one tumor}) = 1 - .95^{20} = .6415$$

Hence in 100 mice one would on the average see 64 with tumors. Monsanto proposes to avoid this "problem" of false positives by analyzing the study" ...at the .01 probability level."

We disagree with the Registrants position. First, even if one did analyze the study at the .01 level as they suggest it would still result (using the same mathematics as before) in seeing 18 mice out of 100 with tumors. And hence one still has the problem of false positives from the registrant's viewpoint. But this causes something worse from a regulatory viewpoint. We have decreased the false positive rate (i.e., the probability of saying that a chemical causes tumors when in fact it does not) at the cost of increasing the false negative rate (i.e., the probability of saying that a chemical doesn't cause tumors when in fact it does). The Registrant wishes to avoid false positives while those concerned with the public health wish to avoid false negatives. Hence, for this reason alone Monsanto's argument is unacceptable.

We further disagree as follows:

1. The two assumptions needed to support the Monsanto argument are themselves in need of support (especially the requirement for statistical independence).
2. False positive results are less likely to occur with rare tumors (ref. 5). And the tumors in question are rare.

Viewpoint is a key issue. Our viewpoint is one of protecting the public health when we see suspicious data. it is not our job to protect registrants from false positives. We sympathyze with the Registrants problem; but they will have to demonstrate that this positive result is false.

Finally, we mention that none of the tumors occurred in the control or low dose groups. Instead there was one at 5000 ppm and 3 at the 30000 ppm dose level. This together with the previous comments make it likely that there is a dose-tumor relationship for Glyphosate.

REFERENCES

1. Letter from Monsanto (signed by Frank. S. Serdy) to EPA (Attn: Robert J. Taylor) dated Feb. 5, 1985.

2. Letter from Monsanto (signed by Robert W. Street) to EPA (Attn: Robert J. Taylor) dated March 20, 1984.

3. J.K. Haseman, et al: Use of Historical Control Data in Carcinogenicity Studies in Rodents - Toxicologic Pathology - 12:126-134. 1984.

4. TOX Branch Memo from William Dykstra to Robert Taylor dated 9/4/84.

5. T.R. Fears et al: False-Positive and False-Negative Rates for Carcinogenicity. Cancer Research. 271:1941-1945. July 1977.

CFR 180.364 Glyphosate Roundup 3/12/05

File last updated 3/12/05

ACCEPTABLE DAILY INTAKE DATA **DRAFT**

RAC, Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	cPI mg/day(60kg)
10.000	200.00	100	0.1000	6.0000

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Grain Crops(64)	0.100	13.79	0.02069
Avocados(6)	0.200	0.03	0.00009
Citrus Fruits(33)	0.200	3.81	0.01144
Coffee(36)	1.000	0.75	0.01119
Grapes, inc raisins(56)	0.100	0.49	0.00074
Leafy Vegetables(80)	0.200	2.76	0.00828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(125)	0.200	2.79	0.00837
Root Crop Veg(138)	0.300	11.00	0.03299
Seed&Pod Veg(143)	0.200	3.56	0.01096
Palm Oil(202)	0.100	0.03	0.00005
Pistachio nuts(210)	0.200	0.13	0.00009
Asparagus(5)	0.200	0.14	0.00043
Bananas(7)	0.200	1.42	0.00426
Olives(104)	0.100	0.06	0.00009
Stone Fruits(151)	0.200	1.25	0.00374
Sugar,cane&beet(154)	2.000	3.64	0.10915
Molasses(96)	20.000	0.03	0.00920
Cranberries(44)	0.200	0.03	0.00009
Cottonseed (oil)(41)	15.000	0.15	0.03375
Kidney(203)	0.500	0.03	0.00023
Liver(211)	0.500	0.03	0.00023
Peanuts(115)	0.100	0.36	0.00054
Guava(184)	0.200	0.03	0.00009
Papayas(109)	0.200	0.03	0.00009
Mangoes(83)	0.200	0.03	0.00009
Soybeans (oil)(148)	6.000	0.92	0.08263
Pineapple(123)	0.100	0.30	0.00044
Fish,shellfish(59)	0.250	1.08	0.00406
Cucurbits(49)	0.100	2.84	0.00426
Fruiting Vegetables(60)	0.100	2.99	0.00449
Small Fruit,berries(146)	0.100	0.83	0.00124
Hops(73)	0.100	0.03	0.00005
Potable Water(198)	0.500	133.33	1.00000
Tea(162)	4.000	0.07	0.00429

cPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.3686 mg/day(1.5kg)	22.81

****

Unpublished,Tox Approved 2F2680,2G2686

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	4.000	0.92	0.05509
Coconut(35)	0.100	0.03	0.00005

	TMRC	% ADI
[illegible] mg/day(60kg)	1.4236 mg/day(1.5kg)	23.73

****

Current Action [illegible]

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Fish,Shellfish(5%)	[illegible]	1.08	[illegible]

ADI	TMRC	% ADI
[illegible] mg/day(60kg)	1.4236 mg/day(1.5kg)	23.73

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EXHIBIT 11

12/4/85

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

December 4, 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: William Dykstra, Ph.D.
Reviewer, Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D. L K.
Pathologist, Toxicology Branch, TS-769

SUBJECT: Glyphosphate — Evaluation of Kidney Tumors in Male Mice.
Chronic Feeding Study.

INTRODUCTION:

Tumors (0 (1)*; 0; 1; 3) were found in the kidneys of male mice at different dose levels. There were differences in the pathologists' opinions as to whether the small localized change in one kidney of the control group (#1028) represented a tumor or not. In order to provide more information, the Agency recommended the preparation of three (3) additional sections from each kidney in the male groups. "The lesion was not present in the recut specimens from that animal" in the control group (#1028). In the final re-evaluation of the questionable control kidney slides (#1028), the conclusion was formulated that "The pathology staff at Bio/dynamics and I (Dr. McConnell) reviewed the lesion and concur that it may be representative of a developing tumor".

MATERIALS AND METHODS:

I (Dr. Kasza, Branch Pathologist) requested all kidney sections from male mice. After selection of slides from all animals in which kidney tumors were diagnosed, I studied them under the microscope.

RESULTS:

There was no difference in diagnoses between my and other pathologists' diagnoses with respect to kidney tumors in mid- (#3023) and high dose (#4029, 4023, 4041) groups. With regard to the questionable male control kidney (#1028), it is my opinion that the presence of a tumor can not definitely be established. My interpretation is similar to the conclusion of Bio/dynamics' pathology staff and Dr. McConnell, that the lesion "may be" a proliferative change having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small well-demarcated focal cell aggregate morphologically different from the healthy looking surrounding kidney tissue, this morphological alteration does not represent a pathophysiologically significant change.

*In parentheses is the review pathologist's findings.

cc: T. Farber
W. Burnam
R. Engler
R. Zendzian

EXHIBIT 12

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

006541

JAN - 5 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - Monsanto Comments to Glyphosate Guidance Document

Caswell No.: 661A
TOX Br. Proj. No.: 7-0773
Record No.: 197157-197162

FROM: William Dykstra William Dykstra 12/18/87
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

and

Theodore M. Farber, Chief Theodore M. Farber 12/28/87
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Requested Action

Review Monsanto's comments relative to Glyphosate Guidance Document (Registration Standard). Monsanto specifically requests a waiver of the inhalation LC_{50} with glyphosate and a waiver of a repeat mouse oncogenicity study with glyphosate.

Conclusions and Recommendations

1. TB concurs with Monsanto's waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

006541

2. TB does not concur with Monsanto regarding the waiver of the repeat mouse oncogenicity study (see discussion in review section).

TB requires that the mouse oncogenicity study be repeated in males only, using larger numbers of animals for each dose level to increase the statistical power of the bioassay. Possibly 200 mice per group may be needed.

For the repeat study the HDT should be 30,000 ppm since, at that dose level, the "equivocal" increase in kidney tumors was observed in the previous study. Additional doses of 15,000 and 7500 ppm are also recommended, which may provide an indication of a possible dose-response relationship.

Other experimental variables should be the same, as much as possible, as the previous mouse oncogenicity study.

A "tier approach" to histopathological examination of tissues/organs will be acceptable. Specifically, sections of kidney and liver should be examined from all high dosage level and control animals. In addition, all grossly observed findings suggestive of possible tumors should also be examined from all animals in all groups in the study. If the above examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should provide a protocol of the repeat study before the experimental work is initiated.

006541

Review

Issue Number I: Acute Inhalation LC_{50} Study With Glyphosate

In the Glyphosate Guidance Document, EPA stated that an acute inhalation study with glyphosate technical has not been submitted and is required.

Monsanto's Response

"There appears to be no justification for an acute inhalation study with glyphosate because: (a) People are not exposed to glyphosate. If any exposure does occur, it is either to the isopropylamine or sodium sesqui salts of glyphosate. Adequate inhalation toxicity studies have been or are being conducted with these end-use materials. The results of available studies indicate a relatively low degree of acute inhalation toxicity; (b) glyphosate is a nonvolatile solid material which is handled in manufacture as a wet cake (10-15% moisture) which precludes any inhalation exposure. We therefore request the Agency concur with Monsanto's opinion that this acute inhalation study is not required per Section 158.135, 81-3 Guidelines since glyphosate is not an inhalable material."

TB Conclusion and Recommendation

TB concurs with the Monsanto waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

Issue Number II: Repeat of the Mouse Oncogenicity Study

In the Glyphosate Guidance Document, the Agency requested a repeat of the chronic feeding/oncogenicity study in mice to fully address the question of ". . . whether the apparent effects noted in the mouse study (renal tubular adenomas) are biologically relevant."

Monsanto's Response

"The results of the mouse bioassay do not provide positive, or even suggestive, evidence of carcinogenicity. The most that can be said is that the results were equivocal as, in fact, the Scientific Advisory Panel stated. Furthermore, the SAP pointed out the fact that this equivocal finding occurred only at a dose level that exceeded the MTD. Quoting from the SAP report, '. . . no oncogenic effect is demonstrated using concurrent controls' and '. . . the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.'

There appears to be no justification for requiring the repeat of a study with equivocal findings at a single site, only at dosage levels exceeding the MTD."

"Several expert toxicologists intimately familiar with the glyphosate chronic/oncogenic mouse study results, and personally involved in the SAP hearing on this issue, were asked to evaluate the need for a repeat study. All experts agreed that additional testing is not justified since the current study was conducted at levels exceeding the MTD and failed to demonstrate a treatment-related oncogenic effect. Their evaluations are enclosed in this part."

"As discussed previously, the fact Monsanto has agreed to repeat the chronic/oncogenic rat study with glyphosate diminishes even further the justification for a repeat mouse study."

"The results of the current rat and mouse studies, along with results to be obtained from a repeat rat study, should be sufficient to assess the oncogenic potential of glyphosate. A repeat mouse study is not necessary."

"Finally, based upon a review of the principles expressed in the Agency's draft 'Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies,' it is clear that the chronic/oncogenic mouse study was conducted at dosage levels which greatly exceeded the upper limit of 7000 ppm required for mouse studies. Furthermore, none of the requirements listed in that document which would necessitate a study are fulfilled for the mouse study (see Attachment 1)."

TB Conclusion and Recommendations

Regarding the need to repeat the mouse oncogenicity study with glyphosate, TB fully concurs with the conclusion and recommendation of the Scientific Advisory Panel (SAP) viz "The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions." In view of the equivocal oncogenic response in the first mouse study, TB believes the oncogenic potential of glyphosate in mice still remains unresolved and that a repeat mouse study is necessary to fully and adequately assess this potential.

TB would also point out that the "Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies," referred to by Monsanto, is a discussion of general principles that may be useful in the interpretation of oncogenic studies and as an aid in determining the need to repeat studies. As such, it is intended to provide guidance rather than rigid rules.

When the circumstances of a particular situation indicate a strict application of the document may be inappropriate, TB will give precedence to what it believes is most prudent for the specific case at hand.

In the case of glyphosate it is recommended that the mouse oncogenicity study be repeated and that the highest dosage level tested be 30,000 ppm, as in the first study, rather than 7000 ppm (or 1000 mg/kg/day) as "suggested" in the MTD document. This dosage level requirement is being imposed to clarify the equivocal results observed at this same dosage level in the first study and in so doing to assess the full potential of glyphosate to induce tumors in mice. It is noted that at this dosage level (30,000 ppm) in the first mouse study, survival of male mice at 24 months was increased compared to male control mice; therefore, this dosage level is not a life-shortening level. It is also recommended that the mid and low dosage levels in the repeat mouse study be 15,000 and 7500 ppm, respectively, rather than 5000 and 1000 ppm as in the first study. The reason for this is to provide an adequate experimental basis for establishing a dose-response relationship if, in fact, a positive oncogenic response came to occur in the repeat study.

In addition, TB recommends that only male mice be tested in the repeat study because the tumors of particular concern, renal tubule adenomas, were only observed in male mice in the first study. However, since renal tubule adenomas are so rare (or at least infrequently observed), TB also recommends that larger numbers of animals be used for each dosage level to increase the statistical power of the bioassay. Possibly, 200 male mice per group may be needed.

TB, then, considers the repeat mouse study to be a specially designed study for the specific purpose of clarifying certain unresolved questions relating to the potential oncogenicity of glyphosate. Hence, the recommendations are that the study be performed at dosage levels of 30,000, 15,000, and 7500 ppm; that only male mice need be tested; and that 200 mice per group may be needed. Similarly, because of the limited nature of the concerns prompting this repeat study, TB will accept a "tier approach" to the pathological examinations in this study. First, a very thorough and complete gross necropsy should be performed on all animals in this study, particularly noting all findings suggestive of possible tumors. Second, a full and complete set of tissues/organs should be excised and fixed from each animal in the study (for possible future need). Third, it will only be necessary in the "first tier" to do the following:

1. Process and examine multiple sections of kidney and liver from all high dosage levels and control animals in the study.

2. Process and examine all grossly observed "findings" suggestive of possible tumors from all animals in all groups in the study.

If the "first tier" examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should be requested to submit a proposed protocol for the repeat mouse study to the Agency for comment before the experimental work is initiated.

Regarding the comments of Monsanto's experts (Drs. Squire, Goodman, and Stemmer), the SAP considered their opinions but nevertheless believed the mouse kidney tumors to be "equivocal" and recommended further studies in rats and/or mice. TB concurs with the viewpoint expressed by the SAP.

EXHIBIT 13

To: Burke, Thomas[Burke.Thomas@epa.gov]
Cc: Bahadori, Tina[Bahadori.Tina@epa.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]
From: Deener, Kathleen
Sent: Tue 5/3/2016 12:05:51 AM
Subject: Re: Issue

Yikes.

Sent from my iPhone

On May 2, 2016, at 7:19 PM, Burke, Thomas <Burke.Thomas@epa.gov> wrote:

> Oh dear.
>
> Thomas A. Burke, PhD, MPH
> Deputy Assistant Administrator
> EPA Science Advisor
> Office of Research and Development
> 202-564-6620
> burke.thomas@epa.gov
>
> Begin forwarded message:
>
> **From:** "Jones, Jim" <Jones.Jim@epa.gov>
> **Date:** May 2, 2016 at 6:29:55 PM EDT
> **To:** Administrator
> **Cc:** "Fritz, Matthew" <Fritz.Matthew@epa.gov>, "Purchia, Liz" <Purchia.Liz@epa.gov>, "Burke, Thomas" <Burke.Thomas@epa.gov>, "Wise, Louise" <Wise.Louise@epa.gov>
> **Subject: Issue**
>
> Administrator, On Friday, the Pesticide Program inadvertently posted on their web page the atrazine eco risk assessment and a glyphosate cancer assessment from last year. The atrazine assessment was posted prematurely as we committed to briefing USDA before releasing and that won't happen for a couple of weeks. We're trying to understand how the gylphosate assessment was even in que for posting as we decided last fall that the assessment was not consistent with the Agency's guidelines and we would convene a new group to reevaluate. The released assessment categorized glyphosate as not likely to be carcinogenic. NGOs saw it and started to post critical reactions. Monsanto saw it and put out a release saying EPA had confirmed glyphosate is not carcinogenic. We pulled down the glyphosate paper as soon as we learned about it. We're working with OPA on a statement which says we are in the middle of our cancer review and we will peer review it this fall before finalizing. The

atrazine assessment will come down shortly as internal government deliberations are not complete. I think we can expect this to "vibrate" for some time.

Jim Jones

Assistant Administrator

Office of Chemical Safety and Pollution Prevention

US EPA

202 564-0342

EXHIBIT 14

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

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

MAR 16 2017

MEMORANDUM

SUBJECT: Transmission of Meeting Minutes and Final Report of the December 13-16, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with EPA's Evaluation of the Carcinogenic Potential of Glyphosate

TO: Rick P. Keigwin, Jr.
Acting Director
Office Pesticides Programs

FROM: Steven M. Knott, M.S.
Acting Executive Secretary
FIFRA SAP Staff
Office of Science Coordination and Policy

THRU: Stanley Barone, Ph.D.
Acting Director
Office of Science Coordination and Policy

Please find attached the meeting minutes and final report of the December 13-16, 2016 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) open public meeting held in Arlington, Virginia. This report addresses a set of scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate.

Attachment

cc:

Wendy Cleland-Hamnett
Louise Wise
Stan Barone
Arnold Layne
Delores Barber
Marietta Echeverria
Michael Goodis
Yu-Ting Guilaran
Steve Knizner
Robert McNally
Wynne Miller
Jaqueline Mosby
Dana Vogel
Gregory Akerman
Jeff Dawson
Anwar Dunbar
Anna Lowit
Cathy Milbourn
Monique Perron
Linda Strauss
OPP Docket

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David A. Jett, PhD
James McManaman, PhD
Joseph Shaw, PhD
Sonya K. Sobrian, PhD

FQPA Science Review Board Members

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Daniel Zelterman, PhD
Luoping Zhang, PhD

FIFRA Scientific Advisory Panel
Meeting Minutes and Final Report
No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center,
One Potomac Yard
Arlington, Virginia

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NOTICE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act (FQPA) Science Review Board members serve the FIFRA SAP on an *ad hoc* basis to assist in reviews conducted by the Panel. These meeting minutes and final report have been written as part of the activities of the FIFRA SAP and represent the views and recommendations of the FIFRA SAP and do not necessarily represent the views and policies of the EPA, or of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the EPA or any party. In preparing the meeting minutes and final report, the FIFRA SAP carefully considered all information provided and presented by the EPA, as well as information presented in public comments.

These meeting minutes and final report of the December 13-16, 2016 FIFRA SAP meeting held to consider and review scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate were certified by James McManaman, Ph.D., FIFRA SAP Chair and Steven Knott, M.S., Designated Federal Official. The minutes and final report are publicly available on the SAP website (https://www.epa.gov/sap) under the heading of "Scientific Advisory Panel Meetings" and in the public e-docket, Docket Identification Number: EPA-HQ-OPP-2016-0385, accessible through the docket portal: https://www.regulations.gov. Further information about FIFRA SAP reports and activities can be obtained from its website at https://www.epa.gov/sap. Interested persons are invited to contact Steven Knott, Designated Federal Official, via email at knott.steven@epa.gov.

SAP Minutes and Final Report No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center
One Potomac Yard
Arlington, Virginia

James McManaman, Ph.D.
FIFRA SAP Chair
FIFRA Scientific Advisory Panel

Date: MAR 16 2017

Steven Knott, M.S.
Designated Federal Official
Office of Science Coordination and Policy, EPA

Steven M. Knott

Date: MAR 16 2017

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FIFRA SAP Chair

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TABLE OF ACRONYMS

ACRONYMS	DESCRIPTION
AAF	2-Acetylaminoflourene
AHS	Agricultural Health Study
AIDS	Acquired Immunodeficiency Syndrome
AOP	Adverse Outcome Pathway
ATS	Academy of Toxicological Sciences
BW	Body Weight
CASAC	Clean Air Science Advisory Committee
CDK	Cyclin-dependent kinase
CI	Confidence Interval
CNV	Gene Copy Number Variation
DABT	Diplomate of the American Board of Toxicology
DNA	Deoxyribonucleic Acid
EFSA	European Food Safety Authority
FACE	Fellow of the American College of Epidemiology
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act of 1996
FRSC	Fellow of the Royal Society of Chemistry
GM	Genetically Modified
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
IARC	International Agency for Research on Cancer
IP	Intraperitoneal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MM	Multiple Myeloma
MOA	Mode of Action
MRID	EPA OPP Master Record Identification Number
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OCSPP	EPA Office of Chemical Safety and Pollution Prevention

ACRONYMS	DESCRIPTION
OECD	Organization for Economic Cooperation and Development
OPP	Office of Pesticide Programs
OR	Odds Ratio
OSHA	Occupational Safety and Health Administration
RR	Relative Risk
SAP	FIFRA Scientific Advisory Panel
SAS	Statistical Analysis System
SCE	Sister Chromatid Exchanges
USDA	United States Department of Agriculture
US EPA or EPA	United States Environmental Protection Agency
WHO	World Health Organization
8-OH-dG	8-hydroxy-2' -deoxyguanosine

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed the meeting minutes and final report of the SAP meeting regarding scientific issues associated with **EPA's evaluation of the carcinogenic potential of glyphosate.** Advance notice of the SAP meeting was published in the *Federal Register* on July 26, 2016 (81 FR 48794).

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. Use of glyphosate in the United States and globally has increased over time, particularly with the introduction of glyphosate-resistant crops; however, usage has stabilized in recent years due to the increased number of weed species becoming resistant to glyphosate. Glyphosate is currently undergoing Registration Review, which is a program where all registered pesticides are reviewed at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act.

Recently, several international agencies have evaluated the carcinogenic potential of glyphosate. In March 2015, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), concluded that glyphosate was "probably carcinogenic to humans" (Group 2A). Later, in November 2015, the European Food Safety Authority (EFSA) concluded that glyphosate was unlikely to pose a carcinogenic hazard to humans. In May 2016, the Joint Food and Agriculture Organization (FAO) / WHO Meeting on Pesticide Residues (JMPR), another subdivision of the WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet.

Recently, EPA collected and analyzed a substantial amount of data informing the carcinogenic potential of glyphosate and utilized its draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment*" (EPA, 2010) to assess its potential carcinogenic hazard. The draft framework provides the foundation for evaluating multiple lines of scientific evidence and includes two key components: (i) Problem formulation and (ii) Use of the mode of action/adverse outcome pathway (MOA/AOP) frameworks. A comprehensive analysis of data on glyphosate from submitted guideline studies and the open literature was performed. This included epidemiological, animal carcinogenicity, genotoxicity, metabolism, and mechanistic studies. Guideline studies were collected for consideration from the toxicological databases for glyphosate and glyphosate salts. A fit-for-purpose systematic review was conducted to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate. Furthermore, the list of studies obtained from the toxicological databases and systematic review was cross-referenced with recent internal reviews, review articles from the open literature, and international agency evaluations (i.e., IARC, EFSA, and JMPR).

Available data from epidemiological, laboratory animal carcinogenicity, and genotoxicity studies were reviewed and evaluated for study quality and results to inform the human carcinogenic potential of glyphosate. Additionally, as described in the draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment,*" the

multiple lines of evidence were integrated in a weight-of-evidence analysis using the modified Bradford Hill Criteria considering concepts such as strength of association, consistency of observations, dose response, temporal concordance, and biological plausibility.

The focus of this SAP meeting was on soliciting advice from the Panel on the evaluation and interpretation of the available data for each line of evidence and the weight-of-evidence analysis, as well as how the available data inform cancer classification descriptors per the Agency's 2005 *Guidelines for Carcinogen Risk Assessment.* The Agency's evaluation is summarized in an Issue Paper entitled: Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs, September 12, 2016 (EPA, 2016a).

During the FIFRA SAP meeting, US EPA personnel provided the following presentations (listed in order of presentation):

Welcome and Opening Remarks – Jack Housenger, Director, Office of Pesticide Programs

Introduction – Dana Vogel, Director, Health Effects Division, Office of Pesticide Programs

Overview of Glyphosate Registration and Carcinogenic Potential Evaluation – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Systematic Review and Data Collection Methods – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Epidemiology Studies – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Animal Carcinogenicity Studies – Anwar Dunbar, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Genetic Toxicity – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Integration and Weight-of-evidence Analysis Across Multiple Lines of Evidence – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

PUBLIC COMMENTS

Oral statements:

During the December 13-16, 2016 FIFRA SAP meeting, oral statements were provided by the following individuals and groups.

1) Daniele Court-Marques, MSPS, on behalf of the European Food Safety Authority (EFSA)

2) Lars Niemann, DVM, on behalf of the German Federal Institute for Risk Assessment (BfR)

3) Donna Farmer, PhD, Caroline Harris, PhD, John Acquavella, PhD, James Bus, PhD, Joe Haseman, PhD., David Kirkland, PhD, and Rick Reiss, PhD, on behalf of Monsanto Company

4) James S. Bus PhD, DABT, Fellow ATS, on behalf of Nufarm Americas Inc.

5) Amechi Chukwudebe, PhD, on behalf of BASF Corporation

6) James S. Bus PhD, DABT, Fellow ATS, and Steven Levine, PhD, on behalf of CropLife America

7) Deborah Hommer, on behalf of Virginians for Medical Freedom

8) Scott Slaughter, on behalf of the Center for Regulatory Effectiveness

9) Sabitha Papineni, PhD, on behalf of Dow AgroSciences

10) Jacob Vukich, PhD, on behalf of DuPont Crop Protection

11) Kevin Hoyer, on behalf of the American Soybean Association

12) Andy Hedgecock, on behalf of FMC Corporation

13) Martin Barbre, on behalf of the National Corn Growers Association

14) Amanda Starbuck, on behalf of Food and Water Watch

15) Bill Freese, on behalf of the Center for Food Safety

16) Robert Hamilton, PhD, on behalf of Sumitomo Chemical

17) Montague Dixon, on behalf of Syngenta Crop Protection

18) Michael Hansen, PhD, on behalf of Consumers Union

19) Sheryl H. Kunickis, PhD, on behalf of the US Department of Agriculture

20) Laura E. Mayer, Marghi Barnes, and Kathy Blum, on behalf of Moms Across America

21) Reverend Billy Talen and Ms. Robin Laverne Wilson, on behalf of The Immediate Life Church

22) Nichelle Harriott, PhD, on behalf of Beyond Pesticides

23) Dalia Hashad, PhD, on behalf of Avaaz

24) Peter Infante, DDS, DrPH, FACE, on behalf of himself

25) David Spak, on behalf of Bayer Crop Science

26) Alexis Baden-Mayer, Esq., on behalf of the Organic Consumers Association

27) Luther Markwart, on behalf of the American Sugarbeet Growers Association

28) James Barile, on behalf of the Natural Resources Defense Council

Handouts provided by oral presenters are available in the public docket at https://www.regulations.gov, docket number EPA-HQ-OPP-2016-0385.

Written statements:

Numerous written public comments were submitted to the FIFRA SAP for the December 13-16, 2016 meeting on EPA's evaluation of the carcinogenic potential of glyphosate. These documents are contained in over 350 docket entries and represent the comments of over 260,000 individuals. These comments are available in the public docket at https://www.regulations.gov, docket number EPA-HQ-OPP-2016-0385. Appendix 1 contains a summary list of these docket entries.

EXECUTIVE SUMMARY

US EPA presented a set of charge questions to the FIFRA SAP covering five broad aspects of the Agency's evaluation of the carcinogenic potential of glyphosate. The questions centered on:

1) the completeness, transparency, and appropriateness of the Agency's methods to collect references for the evaluation;

2) the epidemiological studies investigating the potential for associations between glyphosate exposure and cancer outcomes;

3) the laboratory rodent carcinogenicity studies for glyphosate;

4) assays investigating the genotoxic potential of glyphosate; and

5) the completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate for humans.

The completeness, transparency, and appropriateness of the Agency's methods to collect references for the evaluation

The Panel found that EPA's literature review methods were in general transparent and appropriate. However, the Panel provided several recommendations for updated searches that would be more inclusive and capture more recent, relevant publications. In addition, the Panel recommended that the Issue Paper identify and discuss any rodent cancer bioassays of glyphosate-based formulations. Some members of the Panel proposed that searches of "glyphosate and immunotoxicity" and "non-Hodgkin's lymphoma (NHL) and farming" might be informative. Further, some members of the Panel noted that, since most of the glyphosate in commerce in the U.S. is supplied as the isopropylamine salt, it would be of interest to review whether isopropylamine *per se* or the glyphosate isoproylamine combination has been tested for carcinogenicity, mutagenicity, and immunotoxicity.

Given the importance of epidemiologic data generated by the Agricultural Health Study (AHS), the Panel recommended that EPA contact the AHS investigators to determine whether updated data on incidence of non-Hodgkin's lymphoma (NHL) and other cancers are available. As was discussed at length during the Panel's deliberations, the relevant AHS publication (De Roos et al., 2005) has a limited follow-up period, and so is less informative than it might be were additional and more recent data from this important study-cohort available.

One Panel member was concerned with regard to the sensitivity of the review process. The unusually low number of epidemiological studies identified through searches of PubMed.gov, Science Direct®, and Web of Science™ may indicate that EPA needs to utilize more comprehensive and sensitive techniques in conducting searches of the databases than has been employed to date. It is nonetheless likely that the Agency did identify all of the relevant papers by the combined methods of computerized searching and other means (such as from the reference lists of other relevant papers and reviews).

Some Panel members noted that it is important for the study selection process to involve multiple people independently selecting studies, scoring studies, and then to have a process to reach consensus regarding the selected studies. It was noted that this aspect of the process was not clearly described in the Issue Paper.

Several Panel members noted that it would have been helpful if the Issue Paper had been easier to review. For EPA's Clean Air Science Advisory Committee (CASAC), the Agency produces technical documents for review with references linked using HERONET, a database which provides access to full scientific articles. A Panel member suggested that the Agency do the same for FIFRA-related Issue Papers.

The epidemiological studies investigating the potential for an association between glyphosate exposure and cancer outcomes

The Panel concluded that, overall, the Agency's review and evaluation chose relevant epidemiology studies that inform the assessment of the human carcinogenic potential of glyphosate. The Panel noted that EPA's continuing effort to incorporate human data into risk assessment is commendable. The Panel also found that EPA's evaluation of the epidemiologic studies used a sound, appropriate and acceptable approach, although how the individual study rankings were judged and ultimately how the final rankings incorporating subgroup rankings were determined were not always evident to the Panel without the Agency's explanation. In addition, some Panel members were concerned that important issues that affect the quality ranking of the Agricultural Health Study were not considered. The Panel observed that the agency correctly addressed the issue of both case-control and cohort studies having adequate latency periods as a validity criterion, and pointed out the difficulty of addressing this issue in the absence of reliable data on latency periods for the cancers of interest. However, Panelists had different opinions about the importance of considerations of latency in interpreting epidemiology results.

The Panel recommended that the concept of realized study design should be incorporated into the evaluation of study design. In addition, some Panel members suggested that it may be useful to adopt a classification criterion that separates studies by their 1) design, 2) implementation (which includes consideration of issues such as attempts at full enrollment, completeness of questionnaire design, and completeness of collection of other data) and 3) data analyses characteristics.

Panel members agreed that based on the evidence presented in the Issue Paper (EPA, 2016a), Tables 3.3 and 3.4, there is no reliable evidence of an association between glyphosate exposure and any solid tumor, or between glyphosate exposure and leukemia or Hodgkin's lymphoma, even if the possibility that some of the studies reviewed were subject to potential biases is ignored (such as recall or measurement error bias). However, some Panel members also noted that the epidemiologic data are still limited, and that *none* of the studies is of glyphosate manufacturing workers or others who may be relatively highly exposed. This was felt to be a critical data-gap.

The Panel also agreed with EPA that available studies do not link glyphosate exposure to multiple myeloma (MM). However, one Panel member noted that a recently published meta-

analysis (Chang and Delzell, 2016) reported a meta-estimate of the relative risk for the association between MM and glyphosate of 1.4 (with 95% CI of 1.0-1.9). Another panel member, however, noted that to the extent that the primary study results may be biased high, the meta-statistic will be similarly biased high.

Some Panel members supported the Agency conclusion that "the association between glyphosate exposure and risk of NHL cannot be determined based on the available data," although for somewhat different reasons than provided by EPA. These Panelists believe that all the significant findings from three of five case-control studies and three meta-analyses were most likely a result of recall and other potential biases. Furthermore, the only study not subject to recall bias, the prospective cohort study (De Roos et al. 2005), did not show statistical evidence of a positive association.

Some Panel members emphasized that, as EPA itself has estimated, all available epidemiologic studies of glyphosate-users are not really studies of glyphosate over-exposed workers. These Panel members believe this is a crucial point, and one more reason to doubt that the weakly positive NHL case-control study results are indicative of any genuine biological response due to glyphosate -- as opposed to countless other chemical, biological, microbiological, and antigenic factors associated with living or working on a farm. These Panel members noted that many epidemiological studies have reported farmers to be at increased risk of lymphoma (and sometimes leukemia), including decades before glyphosate was used. One Panel member expanded on this noting that while the Agency correctly considered whether studies had adjusted for exposure to other individual pesticides as one of the important criteria for quality assessment, it has not considered the equally important exposure to farm animals (cattle, pigs, sheep, poultry, etc.) that also needs to be adjusted for in determining the quality of epidemiological studies. These animal exposures involve exposure to oncogenic viruses present in the animals, and also to immune system stimulant endotoxins that are particularly of relevance for tumors of the hematopoietic and lymphatic systems, especially as their occurrences predate the introduction of glyphosate and some of the studies reviewed did show them as important risk factors.

Other Panel members disagreed with the Agency's conclusion, emphasizing the value and importance of the findings reported from several dose-response analyses and meta-analyses. These Panelists noted several considerations including that while the majority of the individual studies are not statistically significant, combining the results using meta-analysis shows a scientifically important and statistically significant elevated NHL risk that is relevant for understanding carcinogenic potential. It appeared to some Panel members that the Agency did not fully consider that the data could be suggestive of a lymphomagenic effect of glyphosate. In particular, some Panel members felt that EPA's discussion of the epidemiological evidence appeared to discount statistical findings and overemphasize non-statistical criteria. Thus, some Panel members believed that there is limited but suggestive evidence of a positive association between glyphosate exposure and risk of NHL. These panelists recommended that the Agency revise their conclusion to something along the lines of the following:

"Based on the weight-of-evidence from epidemiological studies and meta-analyses, the Agency cannot exclude the possibility that observed positive associations between glyphosate

exposure and risk of NHL suggest human carcinogenic potential of glyphosate, even though study limitations and concerns about potential biases remain."

Other Panel members, however, strongly disagreed with such a statement; they instead agreed with EPA that the positive associations with glyphosate reported in some retrospective case-control studies of NHL are (i) too weak and (ii) too likely to be confounded by other aspects of living or working on a farm to be properly considered even as suggestive – especially given the null results in the only available prospective cohort study of pesticide applicators. These panelists noted that if the reported odds-ratios and/or relative risks were instead (i) larger and more precise, and (ii) for some solid tumor-type not otherwise known to appear in excess in farmers, then they would be more persuaded that glyphosate possibly posed a cancer-risk. They also noted that if glyphosate, at the very small exposure levels actually received by farmers, were a bona fide human carcinogen, then the toxic potency of glyphosate in humans would have to be on the order of 100,000 times larger than it has proven to be in numerous studies using laboratory rodents. These panelists knew of no precedent for such a discrepancy – especially for a compound, such as glyphosate, that is (i) poorly absorbed, (ii) non-reactive *per se*, and (iii) not converted *in vivo* to reactive metabolites.

Panel members noted that workers in companies that manufacture, formulate, or handle and sell glyphosate on a wholesale basis comprise a promising resource for epidemiologic study that should be investigated. One panel member noted that there are at least 15 companies that have registered glyphosate products with EPA and suggested that it is likely that large numbers of exposed workers (perhaps many more than those directly involved in manufacturing glyphosate) could be identified for cohort studies in companies involved in the formulation or wholesale handling and sale of glyphosate.

The Panel also provided comments and recommendations regarding the specific criteria including study design, study power, statistical analysis, confounding, statistical bias, recall and selection bias. The Panel discussed at length the possibility that recall bias in retrospective case-control studies can result in over-estimation of the risk of NHL associated with pesticide exposure. Some Panel members felt that key studies show evidence of recall bias, exacerbated in some cases by selection bias, and therefore these studies are not reliable for evaluating the carcinogenicity of glyphosate. Other panel members felt that the necessary data to appropriately evaluate whether recall bias is present or not in the reviewed studies are not available and, in any case, the potential for important impacts of recall bias on the findings could not be reliably separated from those of other potential biases. Another Panel member noted, however, that use of proxy respondents (as necessitated in all retrospective case-control studies when cases are deceased) has been shown to bias cancer risk-estimates above the null (sometimes substantially so), both for pesticides in general and for glyphosate in particular.

The laboratory animal carcinogenicity studies for glyphosate

EPA reviewed and analyzed the results of 15 rodent bioassays and concluded that the results as a whole do not indicate carcinogenicity of glyphosate. Some Panel members agreed with this conclusion, noting that the Issue Paper correctly finds the tumor-response data to be too inconsistent to be considered compound-related. Other Panel members interpreted the totality of the tumor data as supporting the hypothesis that glyphosate may cause the promotion or

progression of common spontaneous lesions. These Panel members argued that there is sufficient evidence to conclude that glyphosate is a weak rodent carcinogen and/or tumor promoter. The Panel noted that holistically interpreting results from 15 rodent cancer bioassays posed a unique challenge.

Overall, the Panel was divided with regard to its interpretation of apparently conflicting evidence from the rodent bioassays of glyphosate. Some Panel members pointed out that true carcinogenic responses should be reproducible, and that the estimated positive results in some of the rodent bioassays of glyphosate were likely to be false positives. These Panelists focused on the lack of consistency among the responses across the entire, unusually large glyphosate database, and the fact that the number of significantly positive results in this large database was no greater than would be expected from random assignment of animals to dose groups. These Panelists also noted EPA's weight-of-evidence ignored the serious multiple comparison problem caused by focusing attention on the most extreme tumor responses without also explicitly noting the many negative dose-response relationships and other null results.

Some Panel members felt that the Agency's weight-of-evidence evaluation gave excessive weight to several factors, including lack of monotonic dose response relationships, historical tumor rates, lack of statistical significance in pair-wise comparisons when there is a significant positive trend, and discounting results at exposures greater than the "limit dose" of 1,000 mg/kg/day. Panelists who disagreed with the Agency's conclusions noted there was considerable heterogeneity between studies that needed to be taken into account. They recommended pooled analyses of multiple studies, within endpoint, gender, and species, as a valid approach to distill the evidence from multiple studies. In support of their conclusion they cited an example, provided in the public comments, of pooled analyses of several endpoints for most of the mouse studies.

Some Panel members felt that the Agency's discounting of statistically-significant trends based on the idea that they were not monotonically increasing was flawed. The Panel noted that a monotonic dose response relationship is not a criterion for a positive rodent response in the Agency's 2005 *Guidelines for Carcinogen Risk Assessment.*

Overall, the Panel concluded that the EPA evaluation does not appear to follow the EPA (2005) *Cancer Guidelines* in several ways, notably for use of historical control data and statistical testing requirements. Regarding historical controls, the Panel noted that the default position should be to *not* rely on historical control data except when concurrent controls yield clearly unreliable results. The Panel recommended that EPA articulate why historical control data were incorporated into some of its analyses and not in others. Regarding statistical testing requirements, the Panel noted that requiring a significant pairwise comparison corrected for the number of pair-wise tests in addition to a significant trend is neither consistent with the 2005 *Guidelines for Carcinogen Risk Assessment* nor a conservative approach for public health protection.

In the view of some Panel members, there are sufficient data to conclude glyphosate is a rodent carcinogen using the approaches recommended to interpret the biological significance of tumor responses in EPA's 2005 *Guidelines for Carcinogen Risk Assessment.* However, other Panel members strongly disagreed with this conclusion finding no reliable and consistent

evidence that glyphosate induces or promotes tumors in laboratory rodents. Some Panel members also did not agree that applying a "conservative test" is necessarily an appropriate scientific goal when evaluating the potential carcinogenicity of glyphosate. Instead these Panel members recommended the standard scientific approach be followed whenever feasible (e.g., apply a decision rule that has a false positive rate equal to the standard rate of 5%).

The Panel concluded that the EPA needs to clarify its position on results from exposures that exceed 1,000 mg/kg/day (the limit dose). Panel members differed regarding the relevance and use of results above the "limit dose" for determining the carcinogenic potential of glyphosate for humans. Some Panel members felt that at high doses homeostatic mechanisms could be overwhelmed, so that results might not be relevant for the much lower levels of exposure experienced by people. Other Panelists noted that since glyphosate is so non-toxic, results at dose-rates that are several-fold larger than the limit dose of 1,000 mg/kg/day could indeed be relevant -- since such doses were still smaller than the maximally tolerated dose. Based on EPA (2005) *Cancer Guidelines*, some members of the Panel concluded it is questionable whether results from exposures greater than 1,000 mg/kg/day, but less than doses corresponding to 5% in diet, should be given less weight. Many members of the Panel concluded not considering or discounting tumor responses at doses that exceed 1,000/mg/kg/day is not consistent with either EPA (2005) *Cancer Guidelines* or standard ways in which bioassay results are typically interpreted. They noted that the limit dose is included in the *guidelines* as a design criterion and it is not advisable to exclude observed data *post hoc* from the analysis and interpretation of experimental results.

Some Panel members agreed that it is important to control for multiple comparisons as described in the EPA *Guidelines for Carcinogen Risk Assessment* (a point noted in public comments as well), but felt that the Agency's specific technique for making this adjustment was flawed. These panelists made specific recommendations for improvements in the analysis.

Other Panelists felt that a multiple comparisons adjustment was not appropriate for addressing the question of whether glyphosate has carcinogenic potential, asserting instead that compelling evidence of carcinogenicity for any tumor-type, regardless of replicability, suffices. These panelists felt that the appropriate method for combining evidence from multiple studies is to use pooled analysis or meta-analytical tools.

Some Panel members believed that differences in study designs could explain some of the tumor response discrepancies, and that, overall, the rodent bioassay data were consistent with glyphosate acting as a weak tumor promoter. There has been no direct test of this hypothesis (such as in a standard initiation-promotion bioassay), and therefore other Panel members felt that such a conclusion was speculative and ignored the lack of reproducibility.

Assays investigating the genotoxic potential of glyphosate

Panel members found that the Agency's overall weight-of-evidence and conclusion that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route are sound. Areas of remaining uncertainty are related to the potential for glyphosate-induced inflammation and genotoxic effects secondary to toxicity caused by high dose exposures (i.e., glyphosate-induced inflammation, oxidative stress, 8-OH-dG, and sister chromatid exchanges or

SCE) and whether the glyphosate-containing formulations have genotoxic potential. In addition, one Panel member noted that none of the assays employed provides an unbiased (global) measure of small insertions, deletions and rearrangements, which can result in gene copy number variation (CNV) and recommended that this section of the Issue Paper be expanded to address this point.

Panel members agreed that the review and evaluation process of genotoxicity studies is sufficient given the limits of the available assays, which are described in the report (first paragraph of section 5.1) as being sufficient to detect: "1) changes in single base pairs, partial, single or multiple genes, or chromosomes, 2) breaks in chromosomes that result in transmissible deletion, duplication or rearrangement of chromosome segments, and 3) mitotic recombination."

Panel members also agreed that, in the determination of whether glyphosate is likely to be genotoxic in humans, the EPA document focuses appropriately on studies conducted in cultured mammalian cells and laboratory animal models.

One Panel member encouraged the agency to consider two key human biomonitoring studies in their evaluation of genotoxicity, specifically studies by Bolognesi et al. (2009) and Koureas et al. (2014).

A few Panel members commented that if glyphosate causes progression of spontaneously arising lesions (in cells carrying cancer driver mutations or other types of DNA damage), then humans may be at risk of glyphosate-induced carcinogenicity, and the longer human lifespan (as compared to rodents) is expected to contribute to the risk. Other members felt that such concerns were speculative.

The completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate

The Panel was asked to comment on the completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate as presented in the Issue Paper, paying attention to how the Agency uses the modified Bradford Hill criteria of strength of association, consistency, dose response, temporal concordance, and biological plausibility in its assessment.

The Panel noted that the conclusion on glyphosate carcinogenicity offered in the Issue Paper has two parts. The first part is a hazard statement while the second part is a risk characterization statement. Since the Issue Paper is not a full risk assessment of technical glyphosate as outlined in the 2005 *Guidelines for Carcinogen Risk Assessment*, the Issue Paper conclusion was assessed by the Panel as a hazard statement.

Completeness: The Panel concluded that the Issue Paper represents a comprehensive review of the available epidemiologic data, laboratory animal bioassay data, and genotoxicity data, but also noted some limitations.

First, the epidemiologic data reviewed in the Issue Paper are limited to users of glyphosate-based herbicides (such as farmers and other herbicide-applicators), but, as EPA estimates, exposures are fairly low – 0.03-7 mg/kg/day for the most highly exposed workers. Published

studies of potentially more highly exposed workers, such as those who manufacture, formulate or are involved in the wholesale handling or selling of glyphosate, are apparently not available.

Second, because the central epidemiologic question with regard to glyphosate is whether its use is associated with risk of developing non-Hodgkin's lymphoma (NHL), some Panel members felt that the Issue Paper would benefit from a broader review of NHL risk-factors that have long been associated with farming.

Third, the Issue Paper does not present potentially relevant data on isopropylamine, despite the fact that most glyphosate in use is as the isopropylamine salt.

Transparency: The Panel found the Issue Paper to be reasonably transparent, although concern was expressed that some of the documents and data used by EPA in this assessment require special procedures for access and a few studies were not available to the Panel or the public. The Agency explained that FIFRA regulations are responsible for some of these limitations. Regardless, the Panel questioned whether the public could fully review and reproduce the conclusions reached by EPA.

Scientific quality: The Panel felt that the scientific quality of the Issue Paper could be improved. Some Panel members pointed to insufficient study design details, incomplete discussions of data limitations, and use of assessment criteria that do not follow EPA (2005) *Cancer Guidelines*. Panel members noted that the health-effects database on glyphosate (from both toxicological and epidemiological studies) poses a somewhat unique challenge, but that the Agency could nonetheless improve upon the scientific quality of its weight-of-evidence approach. For example, several Panel members, and several public commenters, presented methods for formally and holistically assessing the results from the 15 or so laboratory rodent bioassays of glyphosate acid or glyphosate salts that could improve the Agency's approach.

Dose-response and temporal concordance (Bradford Hill Criteria): A number of Panel members did not agree with how the Issue Paper weighed the epidemiological study findings, particularly for NHL, and were skeptical of the report's arguments leading to its conclusion of "no observed association." Not all Panel members agreed with the Issue Paper's conclusion that findings in rodent bioassays are not treatment-related. There was disagreement among the Panel members regarding which analyses/results constituted a significant finding and which instead were false positives. Some panelists disagreed with EPA's assertion that monotonically increasing dose-response relationships were required in order for responses to be considered to be compound-related, and felt that the Agency could better explain its reliance on tumor responses in historical, as opposed to concurrent, control groups. The Panel's consensus was that the Issue Paper needs to refine and strengthen its arguments regarding the weight assigned to "limit dose" responses in the bioassays. The Panel agreed with the Issue Paper's conclusions regarding the lack of genotoxicity effects of glyphosate.

Strength, consistency, and specificity (Bradford Hill Criteria): With regard to the epidemiologic findings, the Panel concurred with the Issue Paper's conclusions regarding solid tumors, leukemia, multiple myeloma and Hodgkin's lymphoma, but differed in their agreement with the Issue Paper's conclusions of no reliable relationship between glyphosate exposure and NHL. The roles and impacts of recall bias, selection bias, residual confounding by other farm

exposures, and reliability of the meta-analyses were all points of disagreement. Several Panel members noted that the epidemiologic database is *unusually uninformative*, in that (i) glyphosate based herbicide-users are not exposed to doses much larger than those ingested by many consumers via their diets, and (ii) the cancer-type that is weakly associated with glyphosate – NHL – has also been linked with farming for many decades, including before use of this herbicide.

The Panel discussed at length the consistency, or lack thereof, of the laboratory rodent bioassay results. Some Panel members suggest that in evaluating the data from the rodent bioassays, dose-response modeling in a pooled analysis would provide a better basis for assessing the consistency and implications of the bioassay results. The current draft instead focuses on each bioassay individually, which obscures readers' abilities to judge whether results are consistent and likely to be compound-related.

Biological plausibility and coherence (Bradford Hill Criteria): Some Panel members felt that the Issue Paper would benefit from a discussion of the hypothesis that glyphosate may be a weak cancer promoter and to explore the immunotoxicity of glyphosate; though not all Panel members felt that having a biologically plausible MOA is a necessary condition to classifying a substance as a carcinogen, as implied in the Issue Paper. The discussion should consider observations of glyphosate treatment-related increases in frequently occurring spontaneous tumors noted in primary study documents (Knezevich and Hogan 1983, Wood 2009b), observations of treatment-related decreases in pre-neoplastic lesions concurrent with increases in tumor frequency in the same organ (Lankas 1981, Knezevich and Hogan, 1983), and significant increases in malignant tumors of treated male rats relative to controls across tumor sites (Atkinson 1993a), which suggest glyphosate may cause promotion or progression of spontaneous pre-neoplastic lesions (also see response to Charge Question 3d).

Uncertainty (Bradford Hill Criterion): The Panel concluded that uncertainties in epidemiological and animal study evidence are well discussed in appropriate sections of the Issue Paper. Uncertainties identified in earlier sections of the Issue Paper, such as excluding formulations with glyphosate and the limitations regarding available pharmacokinetics data, should be expanded upon. Some Panel members noted that in the discussion of the epidemiology findings, the Issue Paper does not adequately assess the likely impacts of potential biases (such as recall and selection) and residual confounding on the odds ratio estimates or the problems that could bias the estimates obtained from the currently available results of the Agricultural Health Study.

Evaluation and Proposed Conclusion: Using a weight-of-evidence approach, the Issue Paper concludes that glyphosate is "not likely to be carcinogenic to humans," especially at reasonably foreseeable dose-rates. Some Panel members agreed with this characterization, while other Panel members felt that the better descriptor for glyphosate is "suggestive evidence of carcinogenic potential." Many Panelists noted that crucial data were equivocal, and that additional data on cancer morbidity and/or mortality from studies of glyphosate-exposed workers would be desirable.

DETAILED PANEL DELIBERATIONS AND RESPONSE TO CHARGE

To seek advice from the SAP regarding EPA's evaluation of the carcinogenic potential of glyphosate, the Agency presented a set of five charge questions to the Panel focused on the evaluation and interpretation of the available data for each line of evidence, the weight-of-evidence analysis, as well as how the available data inform cancer classification descriptors according to the agency's 2005 *Guidelines for Carcinogen Risk Assessment.* Although there are studies available on glyphosate-based pesticide formulations, the agency solicited advice from the SAP on the evaluation of human carcinogenic potential for the active ingredient glyphosate only at this time.

Charge Question 1

The agency has collected a multitude of studies that may inform the human carcinogenic potential of glyphosate through a systematic review of the open literature and toxicological databases for glyphosate and glyphosate salts as described in Section 2.0. Please comment on the agency's methods to collect references for this evaluation, including the completeness, transparency, and appropriateness of these methods. Please also comment on whether there are additional relevant studies that could inform the human carcinogenic potential of glyphosate that were not included in the current evaluation.

Panel Response

The Panel found that EPA's literature review methods were in general transparent and appropriate. The Panel had the following, additional comments.

First, the Panel questioned whether EPA's search strategy was a bit too narrow. For example, EPA's method of searching excluded papers that contained the term "water" which would have omitted papers reporting on studies of the mutagenic or carcinogenic potential of glyphosate in drinking water. The Panel assumed that this was not EPA's intention, and suggested that updated searches be performed without "water" as an exclusion term.

More generally, the Panel recommended that EPA re-run its literature search to capture recent, potentially relevant papers. Several relevant papers have been published since the Issue Paper was released, and these should be reviewed for the final version of the Issue Paper. These manuscripts include reviews by Acquavella et al., 2016, Williams et al., 2016, and several others that will be readily identified by US EPA when it updates its literature search.

The Panel noted at least one paper that would not be picked up by EPA's current search strategy because glyphosate is not mentioned anywhere in the title and the title does not have any of the other search terms that the Panel believes EPA used. The publication is Zhang et al., 2016, "Health effect[s] of agricultural pesticide use in China: implications for the development of GM crops." Published online in Nature, Scientific Reports (October 10, 2016), the study evaluates what the authors consider to be 35 health indicators in Chinese farmers, and differentiates between users of glyphosate-based formulations and users of non-glyphosate based formulations.

Some Panel members noted that it is important for the study selection process to involve more than one person independently selecting studies for review, more than one person independently scoring the studies, and then to come to some consensus regarding the selected studies. One member thought the Agency said that only one person selected the studies. The selection process is usually done by more than one person and then there is a process to come to some consensus regarding the studies that were selected. Another panelist noted that it's very important that there are at least two people selecting and two people scoring the quality, independently. This member noted that the Issue Paper is not clear regarding this important process.

Given the importance of epidemiologic data generated by the Agricultural Health Study (AHS), the Panel recommended that EPA contact the AHS investigators to determine whether updated data on incidence of NHL and other cancers are available. As was discussed at length during the Panel's deliberations, the relevant AHS publication (De Roos et al., 2005) has a limited follow-up period, and would be more informative if additional and more recent data from this important study-cohort are available.

The EPA's Issue Paper states that it is concerned only with glyphosate *per se*, and not with glyphosate-based formulations. But this is not really the case, since relevant epidemiologic studies would be of people who make or use glyphosate-based formulations.

If there are rodent cancer bioassays of glyphosate-based formulations, the Panel recommended that the Issue Paper identify and discuss these. A Panel member noted that, there is at least one such study, which is the republished bioassay of Roundup® by Seralini's group (Seralini et al., 2014). Some Panelists believed that the EPA should have included and discussed this paper, pointing out its strengths and weaknesses and determining what probative value its reported bioassays provide.

There are other studies that may or may not provide relevant and reliable information, and some members of the Panel wanted to make certain that EPA has evaluated these. Some of these, such as Benedetti and colleagues, 2013, were determined by EPA to be "of low quality ranking and not evaluated in detail," but some members of the Panel suggested that EPA might provide some additional detail as to why they were deemed to be uninformative. Other papers from Seralini's group, such as Mesnage et al (2014) and Cox & Surgan (2006), might also be reviewed to determine if they provide relevant and reliable information. At least one Panel member's review, however, indicated that these papers provide no relevant evidence with regard to the Issue Paper.

Some members of the Panel noted that one of the public comments posted at https://www.regulations.gov (document ID number EPA-HQ-OPP-2016-0385-0235, Attachment 6) makes reference to "Epidemiologic studies from the areas in Latin America where glyphosate is sprayed heavily...." This comment may refer to work performed by Dr. Fernando Manas at the National University of Rio Cuarto in Argentina who has studied pesticide sprayers in the soy industry. The comment also refers to researchers from the Pontifical Catholic University, Quito, Ecuador who apparently examined individuals exposed when fields were aerially sprayed to eliminate illicit crops. Some members of the Panel suggested that EPA follow up on these potential data sources.

One Panel member noted that there were 18 studies reviewed for which EPA did not have access to the primary reports, and suggested that these be sequestered and considered separately. Another Panel member did not believe that such sequestration would be required.

Several Panel members noted that it would have been helpful if the Issue Paper had been easier to review. For EPA's Clean Air Science Advisory Committee (CASAC), the Agency produces technical documents for review with references linked using HERONET, a database that provides access to full scientific articles. A Panel member suggested that the Agency do the same for FIFRA-related Issue Papers.

Some members of the Panel suggested that additional literature searches might be useful. The central question that arises from the results of epidemiologic studies is whether glyphosate could be a risk factor for the development of NHL. Many types of lymphomas develop at substantially increased rates in patients with compromised immune systems, such as those with HIV-AIDS, and one working hypothesis is that chemicals that are potent immunotoxicants might also predispose to lymphomagenesis. Some members of the Panel proposed that a search of "glyphosate and immunotoxicity" might be informative, as would a separate section in the Issue Paper discussing glyphosate and immunotoxicity test results.

Some members of the Panel also recommended that EPA run a search using the terms "NHL and farming." Studies dating back many decades have often, though not always, reported that farmers develop NHL at excess rates. One working hypothesis for this is that the antigenic stimuli on farms are very different and more diverse than such stimuli in typical non-farm environments. For cancers of lymphocytes – most of which are plasma cell or B-cell neoplasms – immune-system responses are expected to be central to the process of lymphomagenesis.

Finally, some members of the Panel noted that, since most of the glyphosate in commerce in the U.S. is supplied as the isopropylamine salt, it would be of interest to review whether isopropylamine *per se* or glyphosate isopropylamine salt has been tested for carcinogenicity, mutagenicity, and immunotoxicity.

Charge Question 2

As part of its analysis, the agency has considered 58 individual epidemiological studies investigating the potential for an association between glyphosate exposure and numerous cancer outcomes. Detailed study evaluations were performed to determine overall quality rankings for relevant studies. These evaluations took into consideration study characteristics, including study design, exposure assessment, outcome assessment, control for confounders, statistical analyses, and risk of bias. Twenty-three studies were considered informative with regard to the carcinogenic potential of glyphosate.

a. Please comment on the agency's review and evaluation process of relevant epidemiology studies to inform the human carcinogenic potential of glyphosate.

Panel Response

The EPA's Office of Chemical Safety and Pollution Prevention (OCSPP), guided by the NRC recommendation, conducted a systematic review of the epidemiologic data. The Panel found that the review incorporated a transparent and "fit for purpose" approach in identifying high quality studies for selection that was successfully followed in various stages of the review and evaluation process. The Panel noted that EPA's continuing effort to incorporate human data into risk assessment is commendable.

Review Process

EPA initially identified studies for the review from open literature searches of standard databases (PubMed.gov, Science Direct® and Web of Science™). These searches were supplemented with those from other sources such as registrant generated studies submitted to the agency as required under FIFRA, internal reviews and databases, OPP routine evaluations of the epidemiologic literature, evaluations by OPP and other organizations, other governments, and academia. Although on face value it appears a very comprehensive review had been conducted, some members of the Panel found that there is room for concern over the completeness of the review process for the following reasons:

1) The Panel noted that only 9 of the 58 epidemiologic studies selected for review were identified through searches of PubMed.gov, Science Direct® and Web of Science™. Some panel members suggested that this low yield from these sources is quite unusual, and probably indicates a need for the EPA to utilize much more comprehensive, reliable, sensitive, and effective techniques in conducting searches of these databases than has been employed by the agency for this review. One Panel member noted that many of the key papers do not contain glyphosate in their titles or search terms, and so could not have been picked up by computerized searching, hence the need for more innovative methods to capture the relevant studies in these databases. It is possible nonetheless that the Agency did identify all of the relevant papers by the combined methods of computerized searching and other means (such as from the reference lists of other relevant papers).

2) When asked at the meeting, scientists from the Agency revealed that they did not search for nor did they find studies of workers involved in the manufacture of glyphosate for the review. The Panel noted that, historically, for other chemical and physical agents, it has been studies of manufacturing workers that have contributed predominantly in scientific evaluations of the potential carcinogenicity of chemicals and physical agents that pose threats to the general environment and general population (e.g., benzene, aniline dyes, asbestos). Some of the advantages of this group of workers that have been leveraged before in risk assessment include a) they have considerably much higher exposure levels and wider exposure gradients that permit easier detection of effects if any, than users such as applicators and the general population; b) they comprise a well-defined study group that is easily followed up; c) exposures are usually better documented in company/union work histories than in the self-reports associated with population-based or hospital-based case-control studies that are more prone to misclassification of exposure; d) they can be studied in high quality cohort and nested case-control studies that are in principle much better designs than the usual population or hospital-based case-control studies,

especially for issues such as controlling or eliminating selection bias and other confounding factors; and e) occupational exposures may be relatively free of other confounding exposures.

Panel members noted that workers in companies that manufacture, formulate, or handle and sell glyphosate on a wholesale basis comprise a promising resource that should be investigated. One Panel member noted that there are at least 15 such companies that have registered with EPA and suggested that it is very likely that large numbers of exposed workers (perhaps many more than those directly involved in manufacturing glyphosate) could be identified for cohort studies in companies involved in the formulation or wholesale handling and sale of glyphosate. Exposures among such workers would be expected to be much higher than those experienced by applicators. Some Panel members found it is surprising that for this review, the Agency had not requested registrants to provide data on cohort studies they have conducted, as evidence was presented that at least one manufacturing company had conducted such a study. Some Panel members viewed the inclusion of workers involved in manufacturing, formulation or wholesale handling and selling of chemicals such as glyphosate in studies evaluating the carcinogenicity of these chemicals as vital to the review process. This was suggested to be particularly important, since the Agency's entire review process relied on the assumption that applicators have significantly higher exposures than subjects in the general population. Glyphosate exposure of applicators is estimated by EPA to range from 0.02-0.03 mg/kg/day, whereas the EPA's high-end exposure-estimate for children age 1-2 years (assuming that all relevant foods contained glyphosate-residues at their maximum allowable limits) is 0.47 mg/kg/day (i.e., much higher than that for applicators). Even the estimated highest exposures experienced by glyphosate mixers and loaders of 0.03-7 mg/kg/day overlap with those potentially experienced by children. Thus applicators' occupational exposures may not distinguish them from the general population with regard to absorbed doses of glyphosate, and it is not clear then that epidemiologic studies of such users are of much probative value. Members of the Panel urged EPA, OSHA, NIOSH, and industry to collaborate to identify and study workers with distinctly high levels of glyphosate exposure. Because of its importance, the Agency should consider obtaining data on a cohort study of such workers for revision of the Agency's evaluation.

3) Several Panel members noticed that among 58 individual epidemiological studies reviewed, the agency selected a total of 24 human studies to evaluate the human carcinogenic potential of glyphosate (3 rated as high quality and 21 as moderate) not 23, as stated in the Issue Paper.

4) Some Panel members also suggested that the agency should add a cut-off date (e.g. 12-31-2016) to have a newly published and/or accepted paper considered to be included in the EPA 2016 review.

5) For this review, the Scientific Advisory Panel was charged specifically with evaluating the active ingredient, glyphosate acid. However, all the epidemiological studies collected and considered in the review concerned subjects that were exposed to glyphosate formulations, and there are no studies that reflect exposure to glyphosate acid only. This could affect alignment of the epidemiological with the toxicological findings.

Evaluation Process

In the evaluation of epidemiologic studies, EPA tailored study quality considerations specifically to studies investigating the association between glyphosate exposure and cancer endpoints, with primary literature and associated meta-analyses evaluating the association between glyphosate exposure and a cancer endpoint being the focus of the analysis. The EPA judged each study to be of high, moderate, or low quality in each of six domains: study design, exposure assessment, outcome assessment, confounder control, statistical analysis, and susceptibility to bias. The Panel found that this is a sound, appropriate and acceptable approach, although how the individual rankings were judged and ultimately how the final ranking incorporating these subgroup rankings were derived, were not always evident to the Panel without the Agency's explanation. While the classification of studies in the low quality group appeared to be generally appropriate (see the discussion of Cocco et al. in response to charge question 2d), it was not clear how the separation of the three studies in the high quality group differed from others in the moderate group. Several panelists recommended classifying the studies into only two groups because they did not find it clear that studies in the current high quality group could be meaningfully separated from those in the moderate group. These panelists suggested that the "high" and "moderate" quality groups should be combined into a single group, thus reflecting the opinion by some Panel members that the rating should be merely to provide reasonable qualities of the papers included in the evaluation process.

The Panel observed that the agency correctly addressed the issue of both case-control and cohort studies having adequate latency periods as a validity criterion, and pointed out the difficulty of addressing this issue in the absence of reliable data on latency periods for the cancers of interest in the literature. The Panel noted that choice of the "unexposed" group in case-control studies could be a source of differences in findings among them. For example, using non-farmers as the unexposed group could introduce inherent farmer/non-farmer differences unrelated to pesticide exposure that could be confounding, and suggests that the choice of comparison or reference groups may be another quality criterion.

Regarding the Specific Criteria

Study design

The Panel observed that study design is not as clear cut as the document presents. The single cohort of the AHS by De Roos et al. (2005), is given a higher weight than case-control studies, without regard to other extremely relevant aspects of the realized study designs. The Panel recommended that the concept of realized study design should be incorporated into the evaluation of study design. For instance, for multiple reasons, including the young ages of participants, low cancer incidence rate to date, and selection issues, there are important concerns about the AHS, particularly with the published report (De Roos, et al., 2005), that should be taken into account. The usual higher ranking of cohort studies vis-à-vis case-control studies is not applicable in this particular review. Two of the three studies in the high-quality group are from the same AHS cohort, and as mentioned above, this cohort has certain limitations that do not justify its separation into a higher quality ranking over the studies classified as having "moderate quality." Panel members agreed that a follow-up analysis updating results from this cohort could be quite informative.

Some Panel members suggested that it may be useful to adopt a classification criterion that separates studies by their 1) design, 2) implementation (that includes the consideration of issues such as attempts to get full enrollment, completeness of questionnaire design, and completeness of collection of other data), and 3) data analysis characteristics.

Study Power

Members of the Panel observed that study power could have been given too much weight by the Agency. Once a study has been completed, there is no need for further consideration of power. All the evidence is contained in the effect estimate and its confidence interval (CI). The only time Panel members recommend using this criterion is to omit, *a priori*, those studies that have too few cases to estimate adequately the outcome of interest, with the minimum number of cases defined in advance. A member of the Panel suggested that the issue of sample size/power be separated from the statistical analysis assessment in Table 3.2 and moved to study design.

Statistical Analysis

The Panel suggested that the statistical analysis assessment specifically include handling of missing data, adequacy of the analysis models employed, adjustments for confounding, and other characteristics of good, modern data analysis. In addition, the choice of reference group, as justified in the study design and utilized in the data analysis, has important implications for the interpretation of the results, and should be considered in the ranking process.

Confounding

In the report, the Agency stated that the direction of confounding is to inflate any true effect of glyphosate in the absence of statistical adjustment. The Panel noted that this is not always true, and that numerous studies have shown that the effect of confounding can be in either direction (see for example, De Roos et al., 2005; Hoar et al., 1986 and Zahm et al., 1990). The Panel recommended that the discussion not assume the direction of confounding, but consider utilizing bounds on the role of confounders on the effect estimates. This is particularly important for pesticide co-exposures. The Panel recommended that EPA's consideration of the potential carcinogenic effect of other pesticides be addressed in greater detail.

In the report, the Agency correctly notes and uses in its quality assessment whether a study adjusted for exposure to other individual pesticides. It does not consider when assessing the quality of an epidemiological study whether the analysis adjusts for the equally important factor of exposure to farm animals (cattle, pigs, sheep, poultry, etc.). Animal exposures correlate to potential exposures to oncogenic viruses that may be present in the animals, and to immune system stimulant endotoxins that are particularly of relevance for tumors of the hematopoietic and lymphatic systems. The Panel noted that it is well documented that farmers are at increased risk of leukemia and lymphoma, and this risk existed before the introduction of glyphosate. Moreover, some of the studies reviewed by the Agency clearly show statistically significantly elevated risk of NHL in applicators who also reported exposure to certain farm animals. Thus the Panel concluded that exposure to farm animals is equally important as exposures to other pesticides as potential confounders, and that this exposure needs to be accounted for when assessing risk due to glyphosate.

Statistical Bias

Members of the Panel suggested that EPA (2016a) did not consider in its assessment the potential for statistical bias that is likely to occur when fitting models with too many parameters (see a discussion of this in EPA, 2010). As an example, in De Roos et al. (2005), the pesticide-adjusted estimate for the multiple myeloma outcome is based on an analysis model that uses 23 parameters, 15 of these parameters are to account for exposures to other pesticides. This is an excessive number of parameters for a data set with only 32 cases.

Recall and Selection Biases

The Panel discussed these topics at length because some Panel members were concerned that some of the case-control studies may be biased towards showing an effect of exposure to glyphosate due to recall bias and/or selection bias. Selection bias can occur when the controls in a case-control study are not from the same population as the cases. Recall bias can occur if cases tend to consider more carefully than do controls the questions they are asked regarding their exposures or because the cases have been considering what might have caused their cancer (Breslow and Day 1980, Grimes and Schulz 2002). Recall bias is not a problem in cohort studies or in case-control studies nested in cohort studies insofar as these studies ascertain exposure information before cases became diseased (e.g., tumors are diagnosed). However, in all other case-control studies of glyphosate, information on exposure is based on the memories of cases and controls, or their surrogates.

To investigate the potential for recall bias in epidemiological studies of glyphosate, a Panel member constructed a table that tabulates the number of odds ratios (ORs) or relative risks (RRs) greater or less than 1.0 in each of the 18 glyphosate studies EPA considered to be of moderate or high quality. Most of these ORs and RRs are not for glyphosate, as each of these studies evaluated a large number of pesticides. If recall bias were present it would tend to inflate the ORs of all of these pesticides, not just those for glyphosate. This table shows that, overall, there is a large excess of ORs>1 in those 12 studies potentially subject to recall bias. There is a much smaller excess of ORs>1 in the six cohort and nested case-control studies not subject to recall bias, although all of these studies were based on the Agricultural Health Study (AHS) cohort and hence all used the same questionnaire. Nevertheless, this pattern of ORs is exactly what would be expected if recall bias was a significant problem in these studies.

Moreover, this same Panelist noted that the analyses in the case-control studies of NHL by McDuffie et al. (2001), Hardell et al. (2002) and Erickson et al. (2008) eliminated both cases and controls who had been exposed to certain classes of pesticides from their glyphosate-unexposed groups. This analytical choice could cause selection bias, which will tend to exacerbate the effect of any recall bias present. (It would result in unexposed cases being preferentially removed over unexposed controls.). This Panel member conducted a simulation that demonstrated this effect, which also suggested that in certain cases the effect on elevating ORs could be considerable. This convinced some Panel members that the case-control studies of McDuffie et al. (2001), Hardell et al. (2002) and Erickson et al. (2008) likely suffered from selection bias in addition to recall bias, and therefore these studies, in particular, should not be relied upon for evaluating the carcinogenicity of glyphosate.

There are appropriate statistical methods for adjusting for exposure to other pesticides which were used in many of the other case-control studies of glyphosate. These Panel members recommend that before relying on these three studies, EPA attempt to get the data from these studies reanalyzed using an appropriate method.

This analysis does not imply that these or all case-control studies in general suffer from recall bias. In response to the Panelist's analysis described above, other Panelists noted there are many other reasons why this pattern of results might have been found, including an actual effect of pesticides that was not detectable in the AHS due to its design, follow-up, and analysis. (See the following discussion of the AHS for concerns about that study). Some Panelists thought that reliance on memory of remote exposures to pesticides by NHL cases and controls (especially famers) is particularly prone to recall bias while others did not. These other Panelists pointed to the findings discussed in Blair & Zahm (1993) that argue that recall bias by farmers regarding pesticide use could be less likely than for other exposures. One Panelist, in response, presented additional analyses of the data presented by Blair & Zahm showing that the proportion of controls who succeeded in recalling using any pesticides in response to being probed by an interviewer was identical to the proportion of cases with this recall. This identical pattern of recollection suggests no recall bias for pesticide use. Furthermore, in epidemiological studies, recall bias is but one of multiple potential biases that could affect the findings, and the overall impact of these biases on under- or over-estimation of risk (odds ratios) is hard to predict. Some Panel members felt that the necessary data to appropriately evaluate whether recall bias is present or not in reviewed studies is not available, and in any case, the potential for important impacts of recall bias from pesticide exposures on the findings could not be reliably separated from those of other potential biases, especially interviewer bias. Thus the difficulty in adequately quantifying the presence or absence of these biases, their extent, and impact on risk estimates makes it difficult to address adequately their combined impact on study quality.

Another Panel member noted, however, that several of the case-control studies relied on proxy respondents for information regarding use of glyphosate and other pesticides, and that such reliance (although necessary when cases are deceased) has been shown to lead to very substantial overestimation of odds ratios. For example, in a case-control study of brain cancer in Nebraska, Lee et al. (2005) found that the next-of-kin of brain cancer-decedents were much more likely to report that their loved ones had used glyphosate (and other herbicides and pesticides) than did the live cases themselves. In particular, when the analysis was restricted to responses from live cases, the odds ratio for brain cancer and use of any of the class of herbicides that include glyphosate use was 0.7 (95% CI = 0.2-1.8); but when the analysis relied on next-of-kin as proxies, the odds ratio was 3.4 (95% CI = 1.6-7.3). Lee et al. (2005) thus concluded that they had "found significant associations between some specific agricultural pesticide exposures and the risk of glioma among male farmers but not among female farmers in Nebraska; however, most of the positive associations were limited to proxy respondents. These findings warrant further evaluation in prospective cohort studies where issues of recall bias are not a concern."

The Agricultural Health Study (AHS)

The Panel observed that Koutros et al. (2013) is a cohort study and not a case-control study as stated in the Agency's Issue Paper. The AHS design utilizes recruitment of participants from licensed pesticide applicators. Thus the AHS has the advantage of studying a well-defined

population with presumably higher use of pesticides than any other users. However, the Panel was concerned that important issues that impact the quality ranking of this study were not considered.

The AHS utilizes a "prevalent" cohort, in which subjects are not followed from the time of first exposure. Applicators exposed prior to 1993-1997 who did not make it into the study (for various reasons) may have quite different characteristics, including exposure profiles, than those who are included in the prevalent cohort. This is an important point that was not addressed in EPA's evaluation. It has implications for both the exposure-response and the outcome analyses.

The exposure data collected were for the period prior to 1993-1997 when exposures to glyphosate are assumed to have been low. The exposures measured do not adequately capture possibly much higher exposures cohort members likely experienced after the introduction of transgenic crops in 1995. Failure to update exposure data in follow-up implies that the exposure estimates used in the analysis may be, and are most likely significantly underestimated and there would have been misclassification of exposure. Adding to this effect is the fact that the study design precluded the selection of workers with a short latency.

The Panel had other concerns with the AHS. The cohort is relatively young and the follow-up period is brief, both factors limit the time for sufficient events to occur. There is also the issue of statistical bias mentioned above. See additional discussion of the AHS in response to Charge Question 2d.

Summary

Bearing in mind the concerns expressed above, the Panel concludes that, overall, the Agency's review and evaluation chose relevant epidemiology studies that inform the assessment of the human carcinogenic potential of glyphosate.

b. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and solid tumors, leukemia, and Hodgkin's lymphoma and the agency's conclusion regarding these cancer types described in Section 3.6.

Panel Response

Panel members agreed that based on the evidence presented in the Issue Paper (EPA, 2016a), Tables 3.3 and 3.4, there is essentially no statistical evidence of an association between glyphosate exposure and any solid tumor, or between glyphosate exposure and leukemia or Hodgkin's lymphoma, even if the possibility that some of the studies reviewed were subject to potential biases is ignored (such as recall or measurement error bias). However, some Panel members commented that there were a limited number of available studies to be evaluated in this section and, for some cancer types (e.g., lung, colorectal, breast cancers, etc.), there was only one study available. Therefore, the availability of epidemiologic data is still extremely limited and prevents more in depth discussion of those associations. Additionally, the Panel noted that at the beginning of Section 3.6 (page 63), the Agency mentions one of the 24 epidemiological studies included in the evaluation is uninformative. The Panel requested that the Agency list which study was excluded from the final discussion and conclusion.

Importantly, some Panel members suggested the following points for consideration generally in the reviews of epidemiologic studies: 1) the summaries of all listed relevant studies (Table 3.3) should be expanded to consider topics such as timing of cases and exposure assessment with respect to the registration of glyphosate as well as more details on the exposure assessment; 2) the dose-response summaries should call out comparisons where the referent group was exposed (i.e., the referents were the lowest dose subgroup in the exposed group) or whether there were any exposure lags considered in the analysis; 3) reporting should note the range of risk estimates, as quantified by the range of the CI, and for null effects, including both protective effects and elevated risks, in order to indicate the range of effects consistent with the data; and 4) the discussion should address the conclusions that can be drawn from negative studies. Regarding the last point, Breslow and Day (1987) includes an extensive discussion of the conclusions that can be drawn from negative results in cohort studies. They mention computing confidence limits on estimated excess risk, comparison of the dose levels observed in the study vs. other population exposures, the ability for the risk to have been fully expressed with regard to the time elapsed, the overall risk of the current cohort, and the consistency with other studies.

In summary, the Panel agrees with the Agency's conclusion that there is no evidence of an association between glyphosate exposure and solid tumors, and, there is no evidence of associations between glyphosate exposure and leukemia or Hodgkin's lymphoma. However, the data upon which this evidence is based are very sparse.

c. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and multiple myeloma. Please comment on the agency's conclusion as described in Section 3.6

Panel Response

The Panel believes there are 4, not 5, studies on multiple myeloma (MM), since Pahwa (2012) and Kachuri (2013) are a re-analysis of the same data set; three case-control and 1 cohort, with a total of 67 exposed cases.

None of the case-control studies report a significant association between MM and glyphosate exposure. None of the case-control studies on MM adjusts for exposure to other pesticides, nor to other aspects of farming that may contribute to risk of developing MM. In addition, Brown et al. (1993) excludes farming cases and controls from the "unexposed" category, which may have introduced selection bias.

De Roos et al. (2005) reports a non-significant suggestion of an exposure-response relationship with regard to glyphosate and MM (P-value = 0.17 for trend with cumulative exposure, based on 19 cases of MM). The Panel agreed with EPA that the imprecision of the risk estimates based on such small numbers of MM cases precludes definitive interpretation. The Panel noted that an updated follow up of this cohort of pesticide-applicators is needed, and is hopefully forthcoming. A Panelist also notes that a reanalysis of the MM data from this study was published subsequent to the EPA document which found that an analysis of the full data set that adjusts for lifestyle factors and exposure to other pesticides produces a reduced OR (1.24, 95% CI: 0.52 to 2.94) over the similar analysis in De Roos et al. based on a reduced data set (OR

= 2.6, 95% CI 0.7 to 9.4), and that removal of adjustment for other pesticides has little effect (Sorahan, 2015).

The Panel agrees with EPA that available studies do not link glyphosate exposure to MM. The Panel notes that a meta-analysis (Chang and Delzell 2016) was published subsequently to the EPA document, and the meta-estimate of the relative risk for the association between MM and glyphosate was 1.4 (with 95% CI of 1.0-1.9).

d. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and non-Hodgkin's lymphoma (NHL). Please comment on the agency's conclusion as described in Section 3.6.

Panel Response

In the Issue Paper (EPA 2016a; Section 3.6, page 68), EPA states:

"Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. The agency will continue to monitor the literature for studies and any updates to the AHS will be considered when available."

Based on the six primary studies and three meta-analyses reviewed by the Agency (EPA 2016a), Panel members discussed the strengths and limitations of the available epidemiological data. Some panelists noted that the data were limited by the very low exposures received by study subjects.

The Panel could not reach consensus regarding the Agency's conclusion: some of the Panelists agreed with the Agency and others did not. The disagreement among the Panel members is largely due to their different opinions regarding the relative importance they ascribed to potential biases and other challenges with epidemiological studies that could have affected the reported results, as discussed below. Some stressed that NHL in farmers is uniquely difficult to study epidemiologically, given its long-recognized excess apparently due to factors unrelated to glyphosate. This is why the absence of epidemiologic data on glyphosate manufacturers or others who are, (i) not farmers and (ii) likely to be more highly exposed to glyphosate, would be highly desirable, but is apparently absent.

The Panel's detailed response to this question is organized into three sections: Are all original studies selected and rated acceptably? Are the findings from the epidemiological studies described accurately? and Comments on the Agency's Conclusion.

Are all original studies selected and rated acceptably?

The EPA (2016a) identified six epidemiological studies reporting an association between glyphosate exposure and NHL: five retrospective case-control studies and one prospective cohort study. The EPA applied several criteria (Table 3.1) to rate those studies and assigned two of

them (De Roos et al, 2005 and Eriksson et al, 2008) high quality ratings and the remaining four, moderate quality ratings.

Prospective Cohort Study

De Roos et al. 2005 (reporting on results of the Agricultural Health Study, AHS) is the only prospective cohort study, and it received a high rating from the Agency. This study reports on 92 cases of NHL. The relative risk (RR) reported for ever-never exposure adjusted for age, demographic and lifestyle factors, and other pesticides is 1.1 (0.7–1.9). Thus, while there is no evidence of an association in the results from this study, the results are consistent with both a protective effect and an increased risk. There are several challenges with the use of and interpretation of the AHS findings. These include the role of bias, the cohort selection process, the impact of missing data on the results, and the exposure assessment. Even though this cohort was of pesticide applicators, their likely doses of glyphosate were very small, leading to reduced confidence that the results are reflective of glyphosate *per se*, as opposed to myriad other farm-related factors, several of which are known or suspected to be risk factors for NHL.

Impact of Statistical Bias and Missing Data on the Results

DeRoos et al. (2005) used 8 degrees of freedom to adjust for demographic and lifestyle factors for all outcomes. Because the authors did not find evidence of confounding by other pesticides, they did not have an additional 15 degrees of freedom to adjust for other pesticides in their NHL analyses as in their reported MM results. As noted above, there are 92 NHL cases reported in this study prior to exclusions in the adjusted analysis. Thus the risk of statistical bias due to a small number of responses and a large number of parameters in the analysis model is not as strong for NHL as discussed elsewhere for MM. This consideration is based on the *Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment* (US EPA 2010) that describes statistical bias as going in either direction from models with a large number of parameters and a small sample size (i.e. number of events). Furthermore, it is not known how findings are affected by dropping some cohort members because of missing observations in the adjusted analyses that includes NHL cases in the ever-exposed group. Combining information from Tables 2 and 3 in De Roos, (2005), the Panel noted that it appears 10 exposed cases were dropped from the adjusted analysis (from 71 ever-exposed NHL cases in Table 2 to 61 in Table 3). Some Panel members suggested that a reanalysis be conducted of the full NHL data (i.e. that does not drop cohort members) from De Roos et al. 2005, similar to that conducted by Sorahan 2015 of the MM data from De Roos et al. (2005).

Cohort Selection, Composition, and Follow-Up

The Panel also discussed a concern that the "cross-sectional" enrollment of workers in the AHS could be problematic because it could introduce a survival bias that could bias risk estimates toward the null. This is because pesticide applicators were recruited after their exposure had started and those already diagnosed with cancer were excluded in this prospective study. Another concern is that farmers are known to be at increased baseline risk for NHL. These individuals could be in the reference group in the De Roos et al. (2005) analysis and also exposed to other pesticides, another factor that could increase their baseline risk. The pesticide applicators in the reference group for the glyphosate cohort were most likely exposed to other

pesticides and factors associated with NHL. Thus, even though they addressed adjustment for other pesticides with 15 parameters in their modeling approach, some Panelists thought De Roos et al, (2005) could have underestimated the NHL risk in the ever/never analysis. Some Panel members were concerned that this cohort was followed for an insufficient period of time, and all noted that an updated analysis with additional years of follow up would be informative.

Exposure Assessment

Exposure assessment in the AHS analysis is based on lifetime self-reported pesticide use at baseline, although under- or over-reporting of past exposure is still possible. Using self-administered questionnaires, investigators collected comprehensive use on 22 pesticides and ever/never information on 28 more (De Roos et al., 2005). While the accuracy of self-administered questionnaires relies on individual recall and thorough reporting by respondents, questionnaires are the only feasible tool for exposure assessment in a large cohort such as the AHS. All analyses used one of three exposure metrics: ever/never use, cumulative lifetime use, and intensity-weighted cumulative exposure measured at the time the participant was enrolled in the study. No additional pesticide use is measured after baseline or at any other time during the median of 6.7 years the AHS cohort is followed after enrollment. This poses a challenge to interpretation of the AHS results, if pesticide use varied over time for individual study subjects. The bias introduced by omitting recent exposures is likely to be particularly problematic for the analyses based on cumulative exposure. This omitted exposure bias was only in the direction of under-reporting exposure in the analysis. In other words, many individuals would have been classified in a lower exposure group (including the unexposed group) than was appropriate. These uncertainties can have an important impact on all the dose-response analyses results. Since an exposure lag is typically thought to be appropriate to account for the latency in cancer risk, some Panelists were less concerned about this omission. When exposure lag is taken into account, any exposures within a certain number of years (the lag) before cancer is documented are assumed not to affect cancer risk, where this lag is fixed (and not variable by participant as in the case for the omitted exposure after baseline in the AHS). Although the latency for NHL is unknown, typical exposure lags to account for latency in cancer studies are approximately five years or longer. (See further discussion in the next subsection.)

Furthermore, the Panel noted that the reference group for the dose-response analyses reported in the tables is the lowest tertile of the exposed subgroup, not the more traditional reference being the never-exposed group. De Roos et al (2005) chose to use the lowest exposed tertile in the dose-response analyses in an effort to reduce the potential for residual confounding due to the lack of comparability observed between the never exposed and higher exposed groups. De Roos et al. also conducted analyses using the unexposed group as the reference, and stated that "available data provided evidence of no association between glyphosate exposure and NHL incidence. This conclusion was consistent across analyses using the different exposure metrics and in analyses using either never exposed or low exposed as the referent."

Latency

In cancer studies, concern about latency (or more accurately, empirical induction as defined by Rothman, 1981) is the time between exposure (or the causal action) and the time of disease diagnosis. Panelists had different opinions about the importance of considerations of latency in

interpreting epidemiology results. For instance, Portier et al. (2016) stated that the follow-up period in De Roos et al. (2005; median = 6.7 years) is not long enough to account for cancer latency and this concern was affirmed by some Panelists who indicated that the median observation period of 6.7 years is too short for a sufficient number of cancer events to develop. (Note that the analysis included only incident cases.) One Panel member pointed out that the exposures in this cohort study reflect the entire exposure of the participants throughout their lives up to the time of their enrollment, and consequently these exposures reflect their total lifetime exposure to glyphosate, except for the additional exposure which occurred between enrollment and the follow-up time used in the analysis. Thus, the time between first exposure and the occurrence of NHL is longer than the follow-up period of 6.7 years for most participants. The Issue Paper (EPA 2016a, Section 3.6, page 67) cited the mean and median exposure durations of 7.5 and 8 years at the time of enrollment, respectively, with a standard deviation of 5.3 years. This inference suggests an exposure duration range of 0-18 years at the time of enrollment, with a higher density of exposures being relatively short (because the mean is smaller than the median). Similarly, counting from the 1974 introduction of glyphosate, the potential latency up to enrollment is 20 years. One Panelist noted that another AHS study (Koutros et al, 2013) indicated that the information on both the amount of exposure per year and the years of exposure was collected by AHS so it would be possible to estimate the time of the initial exposure for all participants. Panelists also noted the evidence presented by Weisenburger (1992) who stated that while median latency for NHL is 5-6 years for high exposures to chemotherapy or radiation, it is expected to be much longer for lower exposures. That paper goes on to state that a median range of 15-20 year latency is plausible for lower chronic exposures. Thus, while some AHS participants would have had exposure durations sufficiently long for a NHL diagnosis to manifest, many were much shorter than the median of 15-20 years.

Additionally, one study by Eriksson et al, 2008 that evaluated the latency effect indicated an increase in NHL risk is related to a longer latency period. This study reports that for latency periods less than 10 years, the NHL odds ratio (OR) = 1.11 (95% CI: 0.24-5.08); and, for latency periods more than 10 years, the OR is increased to 2.26 (95% CI: 1.16-4.40). Hardell et al. (2002) reported an increased risk of NHL for a 10-20 year latency period (called induction period in their paper) of 2.32 (95% CI: 1.04-5.16). Longer induction periods also show evidence of increased risk and are relatively stable over time (OR 1.63, 95% CI: 0.87-2.98 for >20-30 year; 1.70, 95% CI: 1.12-2.58 for >30 year).

Despite the limitations of the De Roos et al. (2005) study discussed by the Panel and agreed upon by most, some Panel members consider this study to be the best of the available epidemiology studies. Panelists who considered the other studies weaker did so based mainly on their opinion that retrospective case-control studies are subject to recall bias. Some Panel members suggested this study should be downgraded from a high to a moderate quality rating or that all the studies should receive the same acceptable quality rating. All Panel members agreed that an update from this cohort study would be most welcomed, now that considerably more person-years have accumulated.

Case-Control Studies

The remaining five studies are all retrospective case-control studies (De Roos et al. 2003, Eriksson et al. 2008, Hardell et al. 2002, McDuffie et al. 2001 and Orsi et al. 2009). Most of the

case-control studies (4 out of 5) are rated moderate quality, with the exception of Eriksson, et al. (2008) that is assigned a high quality rating. Some Panelists argued for a single acceptable rating for all studies. One Panel member questioned whether the Eriksson et al. (2008) study should be given the high rating based on the lack of adjustment for demographic characteristics other than gender and age, and the likelihood of a recall or selection bias. The Panel discussed the Cocco et al. (2013) report on a European multi-center case-control study, to which the EPA assigned a low quality rating and as a result excluded it from consideration in its final evaluation. This study examines associations with the major NHL cellular subtype (B-cell), using confirmation of diagnosis by pathologists. Some Panel members suggested that this study should be included in the NHL evaluation in Table 3.4 (page 61) and its rating be upgraded to moderate (if not high) or "acceptable" quality.

Some Panelists, in view of the evidence cited earlier in response to charge question 2a, considered that each of these case-control studies likely suffered from recall bias, which would tend to bias the ORs in the direction of falsely indicating an effect. This is particularly true of McDuffie et al. 2001, Hardell et al. 2002 and Eriksson et al. 2008, which eliminated subjects exposed to certain classes of pesticides from their unexposed groups, a procedure that will, as explained earlier, exacerbate the effect of any recall bias that may be present.

Based on the same study population as McDuffie et al. (2001), Hohenadel et al. (2011) updated the previous study, corrected four misclassified NHL cases, and reported associations with use of glyphosate with or without malathion. The Panel noted that EPA (2016a) did not include or rate the Hohenadel et al. (2011) study, stating that "This study was not included in the study quality ranking because a more complete analysis was conducted by McDuffie et al. (2001)" in Table 3.2 (page 38). The Panel suggests that EPA should discuss the more complete analysis done in the earlier study and describe in detail how the Agency prioritized the McDuffie et al. (2001) study over the Hohenadel et al. (2011) study. However, a recently conducted meta-analysis by Chang and Delzell (2016) reported that meta-RRs of NHL, regardless of whether they were calculated by including McDuffie et al. (2001) or Hohenadel et al. (2011), were essentially the same with a statistically significantly positive association with glyphosate exposure (meta-RRs=1.3 or 1.4, 95% CI: 1.00-1.6 or 1.00-1.8 from Models 2 or 4).

Additional considerations of case-control studies that apply to this topic, particularly concerns about recall and selection biases, are discussed in response to Charge Question 2a above.

Are the findings from the epidemiological studies described accurately?

EPA (2016a) summarized adjusted effect estimates (RR or OR and 95% CI) obtained from six selected epidemiological studies for NHL in Table 3.4 (pages 61-62). Most of the Panel members agreed that the summary data in this table are informative and were presented reasonably accurately and that the data from the ever/never exposure category were repeated in Figure 3.2 (page 64). However, some important findings are missing in the EPA Report. For example, De Roos et al. (2003) reported an overall effect estimate (OR=2.1, 95% CI=1.1-4.0) for the association between glyphosate exposure and NHL in the standard logistic regression analysis, but the Table 3.4 and Figure 3.2 only showed the results (OR=1.6, 95% CI: 0.90-2.8) from an alternative hierarchical regression analysis. Both these analyses were adjusted for co-

exposure to other pesticides but the hierarchical analysis introduced a prior distribution so the analysis shrunk the estimates towards the overall mean of all other estimates. Several Panel members believed that EPA should not use the hierarchical model estimate in Figure 3.2 (and Table 3.4) for De Roos et al. 2003 but, rather, the standard logistic regression estimate because the standard logistic model estimate is more comparable to the estimates reported by all the other studies.

Some Panelists commented on several incorrect or misleading statements in the discussion of NHL studies in section 3.5.2 (pages 55-58). For example, the EPA states for the De Roos et al. 2005 study (page 56): "study participants provided exposure information prior to enrollment and this information was incorporated into the cumulative lifetime and intensity-weighted cumulative exposure metrics. As a result, the amount of time exposed was longer than just the follow-up time since enrollment." As noted previously, this methodology for reconstructing past exposure is non-optimal for this specific study design, which involved subjects who registered as pesticide users. The procedure of recruiting the cohort from current pesticide applicators and then reconstructing their past exposure introduces "survival bias," since only those who were alive and free of NHL at the time of enrollment had a chance to enter the prospective study. If glyphosate exposure causes NHL, this approach to enrollment would have selectively excluded NHL cases. For Hardell et al. (2002; page 57), EPA states: "The wide range of the CI suggests that the analysis is underpowered." The study is statistically significant, and once a study is complete, all the information about power is contained in the effect estimate confidence interval. Some Panelists suggest EPA instead note that the number of exposed cases was small. For McDuffie et al. 2001, at the end of page 57, EPA states: "It would be expected that effect estimates would attenuate if control for co-exposure to other pesticides had been performed." Several Panelists did not agree with this statement; one cannot say what would happen by adjusting for other pesticides since we do not know if their combined effects are additive, multiplicative, or antagonistic, whether the agent is a promoter, and through what mechanisms these compounds act. Regarding the discussion of Orsi (2009; page 58), EPA concludes: "there is potential for selection bias given the study utilized hospital-based controls". Some Panelists questioned why this indicates selection bias. Panelists also requested that, in general, EPA use the term "adjust" instead of "control."

Several Panelists believed that the discussion about changes in risk over time with increasing use of glyphosate (pages 66-67) is also imprecise and potentially misleading. Similarly, the Issue Paper makes claims about magnitudes of risk estimates for studies in countries with higher use that imply a level of understanding about the information used in the various studies, and the basis for the risk estimates, that is not supported by the information in the document or the original papers. Usage estimates only account for trends in sales, and not trends in the more relevant metric of pounds per worker per year, a quantity that is not known. In terms of incidence, there is only one study from which incidence could be determined, and it is De Roos et al. 2005. Therefore, the comparison of temporal trends in glyphosate usage (sales) with estimated effect estimates is potentially misleading and is not informative for judging the adequacy of the reported NHL results.

Thus, some Panel members recommended: 1) adding the missing positive data in the Table 3.4; 2) correcting the imprecise or misleading statements indicated above; and, 3) providing a

more balanced discussion of the NHL findings in EPA's Section 3.6 (pages 63-69) as discussed below.

Exposure-Response Relationship

The data from the forest plot of effect estimates shown in Figure 3.2 (page 64) indicated that the estimates of NHL risks from ever/never exposure to glyphosate in all epidemiological studies, except Orsi et al. 2009 (OR=1.0, 95% CI=0.5–2.2), were above one (RRs or ORs = 1.10–1.85), though none of the estimates that were included were statistically significant (all 95% CI lower bounds were less than 1.00; see the note above about using the standard logistic regression estimate from De Roos et al. (2003) in place of the hierarchical one included). The Panelists had different perspectives on the interpretation of this observation:

1) Since most of these studies (5 out of 6) were case-control studies, residual bias, including recall bias and other possible biases (such as selection bias, measurement error bias, information bias, and any other uncontrolled/unknown confounders, etc.) could each or in combination be operative in some of them. The EPA (2016a) has detailed the "Risk of Bias" (in 3.2.6, page 29-30) and provided a list of possible biases in the study design summary table (Table 3.2, page 34-43). Based on a weight-of-evidence, the agency concluded that it cannot exclude chance and/or bias as an explanation for observed associations in the database. Some Panel members supported this explanation. Other Panelists believed that in spite of the potential for residual bias in all epidemiological studies and notably in case-control studies, the meta-analysis results (detailed below) are a useful summary of the findings as a whole from the six studies of NHL. Meta-analysis is a common approach of distilling the evidence when only a small number of studies, each with limited statistical power, is available.

2) Some Panel members observed that if the association of glyphosate exposure and NHL did not exist, there should not have been any dose-response relationship detected in any studies by any means. In fact, two studies (Eriksson et al., 2008 and McDuffie et al., 2001) reported an increased risk estimate with increased glyphosate exposure, which is discussed below.

3) In addition, some Panel members observed that, due to a small sample size and/or a limited number of NHL cases identified in each of these studies, individual studies had limited statistical power to detect the association even if it existed. In this case, meta-analysis, combining all of those studies into one analysis to increase statistical power, could be the best method to test this scenario, which is also discussed below.

Potential Biases

As is described at length in the response to charge question 2a, one Panel member detailed the potential risk for recall and other biases and believes that in general, the NHL case-control studies in this review are likely tainted by recall bias, particularly, Eriksson et al. (2008), Hardell et al. (2002) and McDuffie et al. (2001). These three studies are singled out because in their analyses both cases and controls who had been exposed to other pesticides from their glyphosate-

unexposed groups are dropped and this may account for the positive associations seen in these studies. This convinced some Panelists that these case-control studies should not be relied upon for evaluating the carcinogenicity of glyphosate, in spite of them receiving an acceptable quality rating. These Panelists recommended that EPA have the data from these three studies reanalyzed using an appropriate methodology before giving any credence to the results from these studies. Other Panel members were concerned that appropriate data for evaluating whether recall bias was an important factor in any study was not available, and therefore its importance cannot be reliably assessed, and suggested the Panel should not put too much weight on it, and that the Panel should not limit its reanalysis recommendation to a subset of studies. Furthermore, as noted by Panelists and discussed by DeRoos et al. (2005), the results of the study by Blair and Zahm (1993) suggest that there is no evidence of recall bias with respect to pesticide use by farmers. On the contrary, even though no single study could provide sufficient evidence of an absence of recall bias in case-control studies of pesticide exposures, one Panelist presented an analysis of data from Blair and Zahm that indicated statistically significant evidence suggestive of recall bias, in part because the exposure effects of interest were stronger and statistically significant when respondents were probed by interviewers. This claim was contradicted by a follow-up analysis by another Panelist who showed that the proportions of cases and controls who improved their recall was identical. This Panelist also noted that the observed findings would be expected if the extra information attributed to recall bias above could actually be a reduction of measurement error. Further discussion of recall bias is provided in the response to charge question 2a.

Another Panelist noted the challenge of statistical bias is present in many of these studies because there are a large number of parameters used to adjust for potential confounding in many of the studies, thus inflating the uncertainty of the effect estimates of interest and resulting in realized bias of estimates in either direction.

To possibly prevent or limit some of these recall and/or selection biases in case-control studies, another Panel member suggested that if the 'unexposed' category was defined for both cases and controls as not exposed to any pesticide, a true baseline reference could be created for the calculation of the NHL risk with exposure to glyphosate versus non-exposure. Thus, there should be no bias in this approach, since the criterion was applied to both cases and controls. This approach would avoid a higher risk of NHL among the unexposed due to other concurrent exposures that could potentially cause NHL. However, another Panel member pointed out that any recall bias present will be exacerbated by eliminating cases and controls from the unexposed group, because, if recall bias is present, removing cases and controls from the unexposed group will preferentially remove cases over controls. This topic was also noted above and discussed at length in the response to charge question 2a.

Other limitations in the five case-control studies noted by EPA (2016a) include: not adjusting for co-exposure to other pesticides (McDuffie et al. 2001 and Orsi et al. 2009), not adjusting for demographic information (Eriksson et al. 2008, Hardell et al. 2002), the potential for selection bias due to exclusion of observations with missing covariate data (De Roos et al. 2003), and selecting controls from a hospital population (Orsi et al. 2009).

Dose-Response

Among all epidemiological studies, three of six were able to break down exposure into different levels. De Roos et al. (2005) assessed cumulative exposure days and intensity-weighted cumulative exposure days by tertile cut points and this approach did not demonstrate any dose-response relationship between glyphosate exposure and NHL. This study used exposure assessed at enrollment only, and the reference group was the lowest exposed group, as determined from participants' self-reported questionnaire responses at baseline. However, two other studies by Eriksson et al., 2008 and McDuffie et al., 2001 did detect a dose-response relationship. Eriksson et al., 2008 reported that for total glyphosate exposure less than 10 days per year, the NHL OR was 1.69 (95% CI: 0.70-4.07); and, for the total exposure more than 10 days per year, the OR was increased to 2.36 (95% CI: 1.04-5.37), indicating a statistically significant positive association. Similarly, McDuffie et al., 2001 reported the NHL OR was increased from 1 (95% CI: 0.63-1.57) for the use of glyphosate 1 to 2 days per year to 2.12 (95% CI: 1.20-3.73) for the use of glyphosate more than 2 days per year. The same study also found a marginally increased risk of NHL of 1.22 (95% CI: 0.96-1.55) due to higher intensity of any pesticide exposure for more than 10 hours per year versus less.

Despite the evidence of a statistically significant dose-response relationship in both studies (Eriksson et al., 2008 and McDuffie et al., 2001), one Panel member considered that these results should be discounted in view of the potential for bias in these case-control studies and other limitations that were previously discussed. However, other Panelists considered that in case-control studies, a dose-response analysis would be the only way to look at changes (i.e., increase) in individual exposure, even if few human studies have this information. Thus, those Panelists believed that the statistically significant dose-responses were important findings, which not only indicated but also further confirmed the exposure-response relationship and which could not and should not be simply discarded or left undiscussed. Furthermore, some Panelists noted that the exposure quantification and dose-response analyses in De Roos et al. (2005) were biased. In particular, this study systematically undercounted cumulative exposure (because exposure almost certainly continued in this population after baseline, but it was not incorporated into the cumulative exposure metrics) and, unlike the studies to which it was compared, the referent group for this analysis was exposed (at the lowest exposure level; vs. unexposed in the other analyses). Thus, the Panel recommended that EPA (2016a) should at least mention and discuss the importance of dose-response findings in addition to just listing those data in Table 3.4 (pages 61-62).

Finally, as described above, the EPA's claim of an apparent lack of temporal concordance in the risk estimates with glyphosate usage patterns, as discussed on pages 66-67 and again on page 129 of the Issue Paper, could be questioned based on the evidence available. See additional discussion of this topic in the third paragraph of the section "Are the findings from the epidemiological studies described accurately?"

Meta-Analyses

The EPA (2016a) Issue Paper accurately identified three meta-analyses conducted, so far, for the association of glyphosate exposure and NHL, and, all three obtained similar and statistically significant positive results. Schinasi and Leon (2014) reported a meta-effect estimate

of 1.5 (95% CI: 1.1, 2.0) in addition to a positive association between glyphosate exposure and B-cell lymphoma (RR=2.0, 95% CI: 1.1, 3.6), a major subtype (85-90%) of NHL.[1] IARC (2015) modified this analysis by including more fully adjusted effect estimates from Hardell et al. (2002) and Eriksson et al. (2008), and obtained a meta-effect estimate of 1.3 (95% CI: 1.03, 1.65). Using the standard logistic regression results (RR=2.1, 95% CI: 1.1-4.0) from the De Roos et al. (2003) study, Chang and Delzell (2016) obtained a meta-effect estimate of 1.3 (95% CI: 1.0, 1.6) in their model 2 and 1.4 (95% CI: 1.0, 1.8) from their model 4. While the same six epidemiological studies as the EPA (2016a) evaluated were included in the model 2, McDuffie et al. (2001) was replaced by Hohenadel et al. (2011) in model 4 of the meta-analysis. Similarly, McDuffie et al. (2001) in model 1 (meta-RR = 1.3, 95% CI = 1.0-1.6) was also replaced by Hohenadel et al. (2011) in the model 3 (meta-RR = 1.3, 95% CI = 1.0-1.7), but Chang and Delzell (2016) used the alternative hierarchical regression data from De Roos et al. (2003) in their models 1 and 3.

Although the selection of studies included and the criteria for the selection varied across the reported meta-analyses, the data used all originated from the same six studies reviewed by EPA (2016a). To clearly document this point and to precisely display individual studies and specific effect estimates selected in the three meta-analyses, a member of the Panel developed the overview table below (Table 1) to compare the meta-analysis findings with the data included in the EPA 2016a Issue Paper (Figure 3.2, page 64). After taking a close look at Table 1, the Panel realized that the EPA data shown in Figure 3.2 of the Issue Paper (EPA, 2016a) were the same as the data from model 1, shown in Figure 1 of Chang and Delzell (2016) in which the results from the alternative hierarchical regression in the De Roos 2003 study were used. Thus, the meta-effect estimate of 1.27 (95% CI: 1.01, 1.59) shown in Table 1, from the model 1 could be added to Figure 3.2 (page 64), and the Issue Paper (EPA, 2016a) should describe this clearly.

Additionally, some members of the Panel noted that the meta-risk estimates and 95% CI in all four models reported in Chang and Delzell (2016) were reported to one decimal place, particularly all the lower 95% CI equal to 1.0, while some of the original studies used two decimals. Therefore, one Panel member re-analyzed the data from the six original studies and updated those meta-risk estimates and 95% CIs to show two decimal places in Table 1. Evidently, three of the four lower 95% CIs shown are more than 1.0 (Table 1). Thus, these three models from Chang and Delzell (2016), in addition to the two other meta-analyses (Schinasi, 2014 and IARC, 2015), showed a statistically significant positive association of glyphosate exposure and increased NHL risk. However, the EPA Issue Paper (2016a) mistakenly concluded (Page 64, Line 3): "All meta-analysis estimates reported were non-statistically significant except the meta-risk ratio reported by IARC (2015), …." In fact, all three meta-analyses show statistically significant meta-RRs with the lower CI >1.00 (except model 3 in Chang and Delzell, 2016). Some panelists suggested that EPA make this correction and consider adding a new Table similar to the Panel's Table 1 to document meta-risk estimate data from all meta-analyses, including the three published ones and possibly the EPA's own meta-analysis as suggested below. The new table will ideally show two decimals for all CIs and clearly present which

[1] See: https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html and/or https://www.seattlecca.org/diseases/non-hodgkins-lymphoma/non-hodgkins-lymphoma-facts/types/b-cell-subtypes.

studies were selected and what conditions each of those meta-analyses included (e.g. study selection criteria and assumptions).

The data presented in Figure 3.2, though only based on the ever/never exposure category, showed individual RRs of 1.00–1.85, all with the lower bound of their 95% CIs < 1.00. The Panel observed that in this case, meta-analysis is the best tool to summarize the findings because it, conceptually, uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree. From multiple sensitivity analyses, all meta-analysis results point to a statistically significant association with the increased risks from 30-50% (meta-RRs=1.3–1.5) for ever exposure to glyphosate. In addition, the meta-analyses consistently show lack of heterogeneity, which speaks for a more robust and credible summary estimate. Some Panelists also suggested that EPA's *post hoc* approach of dividing the studies into the three with higher risks (1.5–1.85) and the three with lower risks (1.00–1.20), in order to argue that the results were contradictory, was not good statistical practice. Meta-analysis is the tool to use to summarize the six study results, particularly in this case where the I^2 statistic indicated low heterogeneity between studies (page 58). The Panel also recommended adding the advantages and reasons of performing meta-analysis in the Issue Paper.

Additionally, some Panel members encouraged EPA to conduct its own meta-analysis and add its meta-RR into the Figure 3.2 forest plot (page 64) for comparison with other published meta-analyses; but other panelists stressed that, since the results from the underlying studies are likely biased high, any meta-statistics would be unreliable. Other Panel members suggested that EPA should conduct a new meta-analysis including all case-control studies (n=5, or n=6 if Cocco, 2013 is included) to prevent heterogeneity of study design and considering the following inclusion criteria: 1) using standard logistic (but not hierarchical) regression; 2) adjusting for other pesticides if available; 3) using the highest exposure dose possible; and 4) using the longest exposure duration possible. The results from this suggested meta-analysis will better address whether or not the exposure to glyphosate in humans, at the highest level and sufficient duration, would increase the NHL risk.

Table 1: Overview of three meta-analyses of glyphosate exposure and NHL, plus individual studies and effect estimates

Studies	Schinasi, 2014	IARC, 2015	Chang & Delzell, 2016[c]				EPA, 2016[d]
			Model 1	Model 2	Model 3	Model 4	
De Roos, 2003	**2.1 (1.1—4.0)[a]**	**2.1 (1.1—4.0)[a]**	1.60 (0.90—2.80)	**2.1 (1.1—4.0)[a]**	1.60 (0.90—2.80)	**2.1 (1.1 — 4.0)[a]**	1.60 (0.90—2.80)
De Roos, 2005	1.1 (0.7—1.9)	1.1 (0.7—1.9)	1.10 (0.70—1.90)	1.10 (0.70—1.90)	1.10 (0.70—1.90)	1.10 (0.70—1.90)	1.10 (0.70—1.90)
Eriksson, 2008	**2.0 (1.1—3.7)[b]**	1.51 (0.77—2.94)	1.51 (0.77—2.94)	1.51 (0.77—2.94)	1.51 (0.77—2.94)	1.51 (0.77—2.94)	1.51 (0.77—2.94)
Hardell, 2002	**3.0 (1.1—8.5)[b]**	1.85 (0.55—6.20)	1.85 (0.55—6.20)	1.85 (0.55—6.20)	1.85 (0.55—6.20)	1.85 (0.55—6.20)	1.85 (0.55—6.20)
Orsi, 2009	1.0 (0.5—2.2)	1.0 (0.5—2.2)	1.00 (0.50—2.20)	1.00 (0.50—2.20)	1.00 (0.50—2.20)	1.00 (0.50—2.20)	1.00 (0.50—2.20)
McDuffie, 2001	1.2 (0.8—1.7)	1.2 (0.8—1.7)	1.20 (0.83—1.74)	1.20 (0.83—1.74)			1.20 (0.83—1.74)
Hohenadel, 2011					1.40 (0.62—3.15)	1.40 (0.62—3.15)	
Meta-RR (95% CI)	**1.5 (1.1—2.0)**	**1.3 (1.03—1.65)**	**1.27 (1.01—1.59)**	**1.30 (1.03—1.64)**	**1.32 (1.00—1.73)**	**1.37 (1.04—1.82)**	**Not yet estimated**

[a] Data presented as effect-estimate (95% CI), standard logistic regression results reported by De Roos, 2003.
[b] Not adjusted for other pesticides.
[c] Four meta-analyses conducted: Models 1 and 3 used *hierarchical* regression but Models 2 and 4 used standard *logistic* regression results from De Roos, 2003; and Models 1 and 2 included McDuffie 2001 but Models 3 and 4 replaced it with Hohenadel 2011.
[d] Data presented in Figure 3.2 (page 64), used *hierarchical* regression in De Roos, 2003 but not indicating any meta-RR.

Some Panel members noted, however, that reliance on the meta-analyses for NHL should be limited by the likelihood of residual confounding in the original studies. These members noted that NHL in particular has long been noted to be elevated in groups of farmers, including in studies pre-dating use of glyphosate. The unfortunate absence of any epidemiologic results from studies of glyphosate manufacturing workers or others who (i) are not farmers and (ii) were distinctly highly exposed to glyphosate renders any causal interpretation of weakly positive results from the available epidemiologic literature highly problematic. These Panel members also believe that the prospective cohort study of pesticide-applicators, although limited in several important respects, is nonetheless more reliable than the retrospective case-control studies.

One Panel member noted that there is evidence (described in the response to charge question 2a) that all studies entering each meta-analysis in Table 1, except for the cohort study of De Roos et al. 2005, are affected by recall bias, which would tend to cause the ORs from these studies to be biased upward. Moreover, as explained in response to charge question 2a, the nonstandard analyses used in Eriksson et al. 2008, Hardell et al. 2003, and McDuffie et al. 2001 would exacerbate the effect of any recall bias present. Each meta-analysis would be similarly biased, and therefore not reliable for evaluating the carcinogenicity of glyphosate.

Other Panel members believed that since all the studies evaluated for NHL were of acceptable quality and three meta-analyses included by EPA show similar positive meta-RRs with uncertainties suggesting the risk estimates are above 1.0, the evidence from human data is suggestive of the carcinogenic potential of glyphosate. All potential biases described above are plausible, but not sufficient for them to disregard the meta-analyses findings. Thus, those Panel members conclude that there is suggestive evidence of a positive association between NHL and glyphosate exposure, which will be discussed below.

Interpretation and Discussion of Results

Some members of the Panel felt that the discussion of the evidence supporting versus not supporting the NHL findings in EPA (2016a) was highly imbalanced. Despite the fact that evaluation of carcinogenicity in humans always relies on epidemiologic studies, with their own strengths and weaknesses, the EPA's overall discussion appeared to focus on weaknesses and limitations of epidemiology in general as well as in each of the specific studies. It appeared to some Panel members that the Agency did not provide any alternative perspective that the evidence could be suggestive of an underlying effect of glyphosate on NHL. In particular, some Panel members observed that EPA's discussion of the evidence appeared to down-weight statistical findings and up-weight non-statistical criteria. For instance, the discussion of the NHL results uses a non-statistical criterion to classify *post hoc* the effect estimates into two groups based on the size of their point estimate while simultaneously down-weighting the meta-analysis results. Some Panel members felt that meta-analysis is the best tool available to summarize the findings of studies considered to be acceptable by the Agency. Some members of the Panel suggested that it is not good practice to do a *post hoc* division of studies based on effect estimates and use this analysis to discount the evidence. They noted that if the studies are sufficient to be evaluated, then it is most appropriate to use a meta-risk estimate as a summary of the findings. Similarly, given the lack of heterogeneity between studies, and the meaningful overlap in effect estimates across the six NHL studies, it would be inappropriate for EPA to conclude that the studies produced contradictory findings, as was done on page 68.

Some members of the Panel suggested that the Agency also did not appropriately interpret the elevated risks in the context of exposure trends or appropriate understanding of what the effect estimates mean. See the discussion of the Agency's temporal concordance argument above in the third paragraph of the section "*Are the findings from the epidemiological studies described accurately?*"

Comments on the Agency's Conclusion

Regarding the epidemiological studies, the EPA (2006) states (in Section 3.6, page 68): "Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. The agency will continue to monitor the literature for studies and any updates to the AHS will be considered when available."

Supporting the Conclusion

Some Panel members supported the Agency's conclusion above, although for somewhat different reasons than provided by EPA, because they believe that all the significant findings from three of five case-control studies and three meta-analyses were most likely a result of recall bias and other potential biases and confounding. Furthermore, the only study not subject to recall bias, the prospective cohort study (De Roos et al. 2005), did not show statistical evidence of a positive association. Thus, they concurred "the association between glyphosate exposure and risk of NHL cannot be determined based on the available data".

Furthermore, some Panel members put heavy emphasis on the magnitude of the exposure estimates. As these Panelists stressed, and as EPA itself estimated, these studies of glyphosate-users are not really studies of glyphosate over-exposed workers. These panel members believe this is a crucial point, and one more reason to doubt that the weakly positive NHL case-control study results are indicative of any genuine biological response due to glyphosate (as opposed to countless other factors associated with living or working on a farm). These Panelists noted that farmers are not exposed to much more glyphosate than the general population. If the small doses of glyphosate that farmers receive were really carcinogenic, then somehow glyphosate would have to be on the order of 100,000 times more potent in humans than is suggested for mice and rats.

Disagreeing with the Conclusion

Other Panel members disagreed with the Agency's conclusion because they accept the value and importance of the findings reported from multiple dose-response analyses and meta-analyses based on the following points:

1) While the majority of the individual studies are not statistically significant, combining the evidence using meta-analysis shows a scientifically important and statistically significant elevated NHL risk that is relevant for understanding carcinogenic potential. This is based on the lower bound of the meta-risk estimate 95% CIs from all three meta-analyses being consistently greater than or equal to 1.0.

2) Despite the fact that a dose-response of an effect from a specific exposure in human studies can be difficult to detect, two case-control studies reported statistically significant dose-response relationships, which indicated an increased NHL risk estimate with increased exposure. These findings provide further suggestive evidence of the carcinogenic potential of glyphosate.

3) The findings from the collection of NHL studies are not contradictory. In fact, the results are quite consistent and suggestive of a positive carcinogenic potential of glyphosate.

4) Assessing potential bias is a challenge that makes the overall evidence base preliminary; overall the NHL result is suggestive of the carcinogenic potential of glyphosate.

After reviewing all selected studies and the Agency's Evaluation (EPA 2016a), the Panel re-addressed the key question in this evaluation:

Whether or not there is the potential of glyphosate-associated NHL risk in exposed humans?

Overall, some Panel members believed that there is limited but suggestive evidence of a positive association between glyphosate exposure and risk of NHL from epidemiological studies. Therefore, those Panelists concluded and recommended the Agency revise their conclusion to use the following statement:

"Based on the weight-of-evidence from all available data that were abstracted from all qualified human studies, the Agency cannot exclude the possibility of observed positive associations between glyphosate exposure and risk of NHL suggesting human carcinogenic potential of glyphosate even though study limitations and concerns about potential biases remain."

Following the EPA (2005) *Guidelines for Cancer Risk Assessment*, the conclusion of "Suggestive Evidence of Carcinogenic Potential" is considered by some Panel members to be the most appropriate because of the descriptors listed to justify this conclusion. Three of the four guideline examples of when this descriptor is appropriate include:

- If a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study does not reach the weight-of-evidence for the descriptor of "Likely to be Carcinogenic to Humans.
- The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system.
- If there is evidence of a positive response in a study whose power, design, or conduct limits the ability to draw confident conclusions (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence.

Some Panel members recommended the following as ways to improve the Issue Paper's discussion of NHL risk:

- Reanalyze the data from all NHL studies using uniform selection and statistical analysis methods.
- Discuss the suggestive association of NHL risk and glyphosate exposure in humans, with the supporting evidence in mouse studies (the positive and monotonic trends of increased lymphomas reported in Wood 2009b, Sugimoto 1997, Knezevich and Hogan 1983 in female mice, as well as Kumar 2001 in male and female mice) and the recent findings on non-genotoxic mechanistic action (e.g. reported from Ford et al., 2017).

Charge Question 3

The agency has followed the 2005 EPA Guidelines for Carcinogen Risk Assessment to evaluate laboratory animal carcinogenicity studies for glyphosate. As described in Sections 4.5 and 4.6, a total of 9 acceptable rat and 6 acceptable mouse carcinogenicity studies were evaluated and considered in the weight-of-evidence analysis. Consistent with the 2005 Guidelines, this analysis took into consideration statistical evidence of a dose-response, the occurrence of corroborating pre-neoplastic lesions or related non-neoplastic lesions to support tumor findings, evidence of progression to malignancy, concurrent and historical control information, and statistical and biological significance of increase tumor incidence, as well as the reproducibility of tumor findings.

a. Please comment on the agency's review and evaluation process of relevant laboratory animal carcinogenicity studies to inform the human carcinogenic potential of glyphosate.

Panel Response

EPA analyzed data from a total of 15 bioassays in mice and rats, noting that many studies showed no compound-related responses, while others showed responses that might or might not reflect compound-related effects. Ultimately, EPA decided that none of the apparently compound-related responses are in fact compound-related, but are instead either false positives or positives only at exceedingly large dose-rates. In discounting these responses, EPA cited some or all of the following factors: 1) lack of monotonically increasing dose-response; 2) absence of pre-neoplastic lesions; 3) incidences in dosed-groups that were within the normal biological variation for a particular tumor type; 4) incidences in the concurrent controls that were not representative of the normal background incidences noted in the historical control animals; and 5) inconsistency in tumor-type-responses in replicate studies.

Panel members disagreed among themselves with EPA's review and evaluation of a total of nine rat and six mice bioassays of glyphosate. In particular, some Panel members focused on individual, statistically significant increases in tumor-responses within individual bioassays, while others focused on the lack of consistency among these responses within the unusually large dataset as a whole. Some Panelists noted that the appropriate approach to evaluate the evidence provided by the collection of findings across multiple studies is to combine endpoint-specific data or results (within gender and species) in pooled analyses, such as meta-analyses. Some panelists suggested that adjustments for different study durations be incorporated in these pooled analyses. It is important that endpoints, species, and genders not be combined in either pooled or meta-analyses because 1) this violates the spirit of the guidelines and 2) the scientific interest is whether there is any carcinogenic potential in any organ that is relevant to humans. All acceptable studies for each outcome analyzed should be reported in the document.

Given the large number of bioassays, the Panel suggested that the EPA Issue Paper might benefit from a holistic presentation and discussion of each tumor-type that appeared to be glyphosate-related in one or more bioassays. This would be consistent with current guidance to use a weight-of-evidence approach to analyze and assimilate all relevant data. This approach mandates use of professional judgment, and may well lead to different conclusions depending on differing but equally well-justified decision rules.

One Panel member considered the Agency's approach for applying the 2005 *Guidelines for Carcinogen Risk Assessment* to the assessment of the glyphosate rodent carcinogenicity data to be flawed, and additional Panelists agreed with this perspective. This Panel member did not find the statistical approaches employed to be consistent with evaluation methods used by other authoritative bodies (e.g., the National Toxicology Program, because the analysis did not include correction for survival) and concluded that at least some of the statistically-significant Cochran-Armitage trend tests and unadjusted pairwise comparisons should be considered to be compound-related (specifically ones that occurred with *P-values* of 0.01 or below).

Many Panel members concluded that the Agency's discounting of statistically-significant trends based on the idea that they were not monotonic was flawed. Regarding statistical evidence of a dose-response, the EPA document discounted four positive tumor responses (tumors with a significant Cochran-Armitage trend test), in part, because the tumor responses were considered non-monotonic. The document discounted three additional positive tumor responses because the dose response was considered shallow. However, the Panel noted that monotonic dose response is not identified as a criterion for a positive rodent response in the EPA's 2005 *Guidelines for Carcinogen Risk Assessment.*

One Panelist noted that it is not good practice to discount the highest dose in these studies, the dose at or above the limit dose, as not relevant to humans. Toxicological studies are designed to detect carcinogenic effects over a range of doses. Sufficiently high doses are needed in order to ensure these studies will be sensitive to the effects of the study compound. The limit dose is used as guidance for study design to determine the highest dose to be studied. This panelist expressed the view that it is not acceptable to selectively discount doses studied in a hazard assessment merely because they are at or above the limit dose. See further discussion of the use of the limit dose in response to Charge Question 3f.

The OECD Test Guidelines 451, 452, and 453 state, "Selection should make provision for survival adjustments, if needed." According to FDA's Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, "the effects of differences in longevity on numbers of tumor-bearing animals can be very substantial, and so, whether or not they (the effects) appear to be, they should routinely be corrected when presenting experimental results." OECD Guidance Document #116, section 4 (page 17) refers to the Cochran-Armitage trend test and states, "Problems arise if there are differences in mortality between the groups. The test is sensitive to increases in treatment related lethality and this leads to an incorrect level of the Type I error (the risk of falsely rejecting the null hypothesis)."

The Glyphosate Issue Paper discusses the lack of reproducibility of significant tumor findings across studies, but did not, in the opinion of many Panel members, provide sufficient discussion of the technical and biological differences that make bioassays performed internationally over a 36-year period unlikely to be true replicates. Also, the Glyphosate Issue Paper does not clearly define the approach or criteria used to identify significant findings across studies. Some Panel members noted a number of places where missing clear definitions/criteria may be responsible for dismissal of significant increases in benign and malignant neoplasms as not being compound-related. Specifically, these panelists noted:

1. The decision to use historical controls did not seem to have been made *a priori* using pre-specified criteria. As a result, the Issue Paper findings appear to have not followed EPA's own guidelines which state, "...statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average." The Agency used this argument to dismiss increased incidences in the treated groups in several studies. Guidelines also caution against simply relying on a range of the historical responses "... because the range ignores differences in survival of animals among studies and is related to the number of studies in the database." The

suggestion to use historical data gathered within two to three years of the study under review is not followed in evaluating Wood et al. (2009b), since historical controls are from data generated almost a decade earlier from 1987 to 2000. [See EPA (2005) *Guidelines for Carcinogen Risk Assessment* section 2.2.2.1.3., Concurrent and historical controls.]

2. Although the purpose of two or more lower doses is to provide information on the shape of the dose response curve. EPA guidance specifies use of the Cochran-Armitage test to examine whether the results in all dose groups together increase as dose increases. The Cochran-Armitage test is most powerful in identifying significant trend when the underlying trend is linear, but a significant test finding does not imply a linear dose structure, only an increasing response with increasing dose (i.e., an increasing dose-response relationship). In a number of animal studies on glyphosate, the response at doses above 1,000 mg/kg deviated significantly from the near linear trend observed when considering the control and only the remaining lower doses. Decreases in the significance of the tested trend when the highest dose-responses were included in the Cochran-Armitage test could reflect differences in toxicokinetics and/or toxicodynamics at doses above the 1,000 mg/kg dose EPA considered the limit dose for glyphosate.

3. Significant increasing trends as identified by the Cochran-Armitage test, without correspondingly significant pair-wise comparisons test results were also observed with the animal toxicology studies. The Issue Paper discussion often discounts the importance of statistically significant trend test findings when there are no correspondingly significant pair-wise comparisons. This decision rule does not appear to agree with that specified in EPA's guidelines which specify that significance in either of the tests should be considered evidence of significant dose response (i.e., conclude significant response if either Test A OR Test B is significant). While the Sidak adjustment is used to protect against Type I (false positive) indications, this adjustment may also increase the probability of a false negative outcome.

The Agency invoked a four-part "AND" rule: *concluding a significant dose response if one of the pairwise comparisons was significant AND the Cochran-Armitage tests is significant AND the observed trend appears monotonic AND the observed control response rate does not greatly deviate from historical controls levels when available.* Otherwise, one concludes that the dose-response is not significant, as was done in the Issue Paper. These issues lead to the following findings being specified as not treatment related: (77% of the studies cited).

Rats

- Lankas (1981): interstitial cell tumors in testes at 31 mg/kg/day group; pancreatic islet cell adenoma in males; reticulum cell sarcoma in spleen in females.

- Stout & Ruecker (1990): pancreatic islet cell adenomas (males); liver adenomas (males) thyroid cell adenomas (females)

- Brammer (2001): liver adenomas (males)

• Wood et al. (2009a): significant trend for adenocarcinoma and adenoma/adenocarcinoma combined (females).

Mice

• Atkinson et al. (1993b): Hemangiosarcoma in males: Significant trend and significant unadjusted pairwise comparison between the control and high dose groups.

• Wood et al. (2009b): Significant trend for bronchiolar-alveolar adenocarcinoma (males) Significant trend for Malignant Lymphoma (males).

• Sugimoto (1997): Significant trend in hemangioma incidences (females).

Some Panel members noted that the tumor-response data were markedly inconsistent within this unusually large set of bioassay results. For example, at least one Panel member noted and expressed concern the statistically significant report of testicular interstitial tumors (that is, Leydig cell tumors) in one group of Sprague-Dawley rats exposed to glyphosate at a dose-rate of only 31 mg/kg/day was not found important. But another Panel member noted that consideration of the dataset consisting of responses from 8 rat bioassays (Williams et al., 2016) shows there is no relationship between dose and tumor incidence across rat tumor bioassays.

This type of analysis is presented for multiple tumor-types in Williams et al. (2016), and/or could be created by EPA. The Panel recommended that although not a guideline practice, such tabulations, properly analyzed, might form a better basis for EPA's weight-of-evidence evaluation of glyphosate's carcinogenic effects in laboratory rats and mice. Some Panel members while supporting this approach in general expressed doubt that such an analysis would be meaningful, given that the bioassays were performed internationally and over a 36-year time span.

In summary, many Panelists concluded that the Issue Paper's protocol for assessing the significance of laboratory animal carcinogenicity study results does not appear to have followed Agency guidelines. In addition to misinterpreting the rule on assessing significance from combined multiple comparison tests and the Cochran-Armitage trend test, the Issue Paper incorporates into the protocol criteria such as

- exclusion of dose levels considered above the limit dose, without documenting findings that demonstrate that the limit dose was actually exceeded,
- requiring visual confirmation of a monotonic trend in scatter plots of data, which is known to be a poor way of assessing trend, and
- subjectively incorporating information about historical control levels without following other Agency guidance on how and when to incorporate this information.

Many Panelists felt that a more systematic review of the data, organized by endpoint, and that includes in addition to study-specific analyses, a formal statistical analyses of data pooled from all pertinent and quality studies, would result in a stronger assessment.

b. For some of the available animal studies, statistically significant trends in tumor incidence were observed with a lack of statistically significant pairwise comparisons when adjusted for multiple comparisons[2]. Please comment on the agency's methodology and interpretation of statistical analyses to evaluate a linear dose-response (trend test) and increased tumor incidence as compared to controls (pairwise comparisons).

Panel Response

As discussed in Question 3a, many Panelists did not agree with the Issue Paper's methodology and interpretation of statistical analyses to evaluate dose-response and increased tumor incidence as compared to controls. The assessment considered each study separately and required that it show evidence of all of the following (the four-part "AND" rule), *at least one of the Sidak pairwise comparisons was significant AND the Cochran-Armitage test is significant AND the observed trend appears monotonic AND the observed control response rate does not greatly deviate from historical control level when available.*

In this response, the Panel first directly addresses EPA's methodology and interpretation based on the 2005 Guidelines. The Panel suggests alternative approaches to statistical analyses that are not specified in the Guidelines, but that could be considered in future guidelines.

Panel comments directly addressing EPA's use of the 2005 Guidelines for Carcinogen Risk Assessment

According to EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, either a significant trend (Cochran-Armitage) test finding or a statistically significant increase of a treatment group response above its corresponding control group response is sufficient for establishing a finding of a significant treatment-related effect. The document states: "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result" (page 2-19). In requiring that significance be achieved in BOTH tests, the Panel concluded that the Issue Paper's protocol did not follow the 2005 *Guidelines*.

The 2005 *Cancer Guidelines* state that "Considerations of multiple comparisons should also be taken into account. Haseman (1983) analyzed typical animal bioassays that tested both sexes of two species and concluded that, because of multiple comparisons, a single tumor increase for a species-sex-site combination that is statistically significant at the 1% level for common tumors or 5% for rare tumors corresponds to a 7–8% significance level for the study as a whole. **Therefore, animal bioassays presenting only one significant result that falls short of the 1% level for a common tumor should be treated with caution**" (p 2-20).

The remainder of this section addresses three distinct Panel perspectives on the use of the 2005 *Cancer Guidelines* with regard to the large number of studies being reviewed and how multiple comparisons should be handled.

Some on the Panel read the first line of the 2005 Guideline quote above as not mandating the use of multiple comparison tests but leaving its use to the discretion of the analyst. Others on

[2] Individual studies include Stout and Ruecker (1990), Brammer (2001), Wood et al. (2009a), Atkinson (1993b), Wood et al. (2009b), Sugimoto (1997). Results are summarized in EPA's Issue Paper, Table 4.11 and Table 4.18.

the Panel interpreted the line as specifically requiring analysts to account for multiple comparisons (to consider both comparison-wise and experiment-wise errors) in assessing the findings from one or more studies. After extensive discussion, the Panel agreed to recommend that EPA further clarify this statement and make explicit its requirements in this matter.

It was the opinion of some on the Panel that the last line of the 2005 *Guidelines* statement is the driver for a decision rule implemented in the Issue Paper that "down-weights" multiple comparison findings where the associated comparison P-value is greater than 0.01. Logically this rule implies that studies where significant comparisons are observed in multiple tumor types, or where more than one comparison in a single tumor is significant would not have findings "down-weighted" (that is, treated with caution), but would be considered as evidence of a significant dose response. In the Issue Paper, this rule resulted in most study findings being down weighted.

Operationally, by only considering Sidak-adjusted comparisons with a P-value less than 0.01 as significant and worthy of discussion (i.e. as having "weight") a number of findings considered significant by some on the Panel were not discussed. This included:

1) Pancreatic Islet Cell Adenomas and Combined Adenomas and Carcinomas in male Sprague-Dawley rats (Stout & Ruecker: [MRID 41643801])

2) Hemangiosarcomas in Male CD-1 Mice (Atkinson [MRID 49631702])

3) Liver Adenomas in Male Wistar Rats (Brammer [MRID: 49704601]),

4) Mammary gland adenomas/adenocarcinomas combined in female Wistar rats (Wood [MRID: 49957404]),

5) Malignant Lymphomas in Male and Female CD-1 Mice (Wood [MRID: 49957402], and

6) Hemangioma in male and female Specific-Pathogen-Free (SPF) ICR (Crj: CD-1) mice (Sugimoto [MRID: 50017108 and 50017109]).

Thus, in the view of some Panel members, the findings above are sufficient evidence to conclude glyphosate is a rodent carcinogen using the approaches recommended to interpret the biological significance of tumor responses in EPA's 2005 *Guidelines for Carcinogen Risk Assessment.*

Other Panel members, embracing the Issue Paper's use of multiple comparison test controls, concluded that the laboratory animal toxicology studies provide no evidence that glyphosate is a rodent carcinogen. In support of their conclusions, they noted that the animal data on glyphosate encompass 15 bioassays that each employ a control group and three or four treated groups of males and females of rats or mice that combined make up 30 sex-species groups studied. This glyphosate dataset is far more extensive than the NTP bioassay data upon which the Haseman (1983) finding is based. Concern was expressed that the 1% rule may not be adequate for correcting for multiple comparisons in this complex glyphosate data base.

Dr. Haseman, in his presentation to the Panel, showed that the numbers of significant comparison-wise *P-values* at both the 5% and the 1% level in the glyphosate bioassays are no

greater than would be expected purely by chance under the null hypothesis of no treatment effect, when conducting so many statistical tests (i.e., tests from so many different studies by sex by comparisons within tumors).

One Panel member noted that the FDA does not require analysts to use multiple comparison procedures to adjust comparison-wise significance levels but instead sets a small P-value of 0.005 as its cutoff level for establishing significance. There are statistical methods to account for multiple comparisons, and these provide valid statistical tests for use in animal bioassays that properly control the false positive rate (Benjamini and Hochberg 1995, Farrar and Crump 1988, Westfall and Young 1989). Absent results from such tests, the analysis presented to the Panel by Dr. Haseman (discussed above) is another approach for determining whether the number of significant individual comparison tests observed are more or less than would be expected by chance. If there are more than expected, one can conclude that there are statistically significant dose responses in the database, otherwise, one can conclude that there is little evidence.

It was noted that one rat bioassay (Stout and Reucker, 1990) produced three significant tumor observations, which was greater than the number expected by chance. In discussion with the Panel, Dr. Haseman confirmed that the National Toxicology Program has a practice of upgrading (up-weighting) initially non-significant findings (those with a P-value of 0.05 for common tumor types) to "equivocal" when multiple tumors are observed.

The Panel also discussed the importance of consistency of tumor responses across multiple assays as another criterion for assessing the significance of individual outcomes. The Issue Paper handles this issue in an ad hoc fashion, which some Panelists considered appropriate given EPA did not apply formal statistical tests that corrected for multiple comparisons.

To augment EPA's evaluation of consistency among bioassays, one Panel member reported on an analysis they conducted where all of the significant tumor responses in rodent bioassays identified in the issue paper were compared across studies. Responses were compared within the same sex, species and strain of rodent. The only significant tumor response among the ten identified in the Issue Paper that had some support across studies was malignant lymphomas in male CD-1 mice. Wood et al. (2009b) reported a significant dose response trend (P-value=0.0066, high dose $\approx$ 900 mg/kg/day) as did Sugimoto (1997, P-value=0.016, high dose $\approx$ 4200 mg/kg/day). However, Wood et al. noted a significant excess response (5/51) at the highest tested dose of 810 mg/kg/day, whereas Sugimoto reported no tumors (0/50) at a comparable dose of 838 mg/kg/day. Knezevich and Hogan (1983, high dose $\approx$ 5000 mg/kg/day) found no evidence of an effect at any dose tested (P-value = 0.75). Thus the response at the high dose in Wood et al. (2009b) was not reproduced in Sugimoto (1997), and neither the response in Wood nor that in Sugimoto was reproduced in the Knezevich and Hogan study.

After reviewing all the significant tumor responses for consistency, the Panelist who conducted this review concluded that none of the positive findings analyzed in the Issue Paper were reproduced in other studies.

Due to the multiple comparisons evaluations described above, coupled with the lack of consistency among studies, some Panel members concluded that the significant responses that

were observed in the animal studies appeared to best be interpreted as the results of random assignment of animals to dose groups rather than due to any carcinogenic effect of glyphosate. In the view of these Panelists, the interpretation that led to this conclusion is consistent with the 2005 EPA *Cancer Guidelines*. These Panel members also did not agree that applying a "conservative test" is necessarily an appropriate scientific goal when evaluating the potential carcinogenicity of glyphosate. When one uses conservatism of a test as a criterion, there is no clear stopping point, as a more conservative test can always be found. Instead these Panel members recommended the standard scientific approach be followed as nearly as possible (apply a decision rule that has a false positive rate equal to the standard rate of 5%, and otherwise is as powerful as possible).

Representing the third point of view, some Panelists felt that a multiple comparisons adjustment was not appropriate for addressing the scientific question of whether glyphosate has carcinogenic potential from the animal toxicology studies. These Panelists believe that the most important and relevant scientific question is not whether there is compelling scientific evidence of cancer when all cancer endpoints (across all species, and genders) are examined together but **whether there is compelling evidence of carcinogenicity in any one of the endpoints in any single species or gender.** For these Panelist, the analysis should be performed for each cancer endpoint by species by gender combination separately, and data from all relevant studies should be pooled and examined in one omnibus analysis that accounts for study differences. The analysis transmitted as written comments to the Panel by Dr. Christopher Portier, provided a series of examples of such pooled analyses. These are discussed in more detail at the end of the next section.

Additional Panel comments

The Panel also commented more generally on broader statistical issues relevant to the methods and goals described in the 2005 EPA *Guidelines*. It was pointed out that the scientific interest is to assess whether there is a monotonic dose-response trend in the underlying (unobservable) population. Even if the true dose response trend is increasing monotonic, some Panel members suggested that there is no reason to expect a scatter plot of the raw response data to display an increasing monotonic pattern. The Issue Paper confuses the expected underlying rate trend with the observed empirical rate trend. There is a non-negligible probability of observing a non-monotone response when the true underlying response is monotone, primarily due to sampling variability. This was illustrated by one Panel member who presented two realistic situations in which the true dose response was monotone but the observed dose response is non-monotone more often than not. The Panel observed that the non-monotonicity of an observed dose response typically provides very little evidence that the true dose response is non-monotone. Consequently, to some Panel members, the non-monotonicity of the observed dose rate data cannot be used as a valid criterion for down-weighting the results of formal statistical tests that do indicate significant trend.

Unlike pairwise tests, trend tests incorporate all of the dose response data in a single test, and therefore can have greater power for detecting effects than pairwise comparisons. When a trend test and pair-wise comparisons are used together, it could be logically argued the result of the trend test should also be included in the count of multiple comparisons, and the trend test P-value should also be adjusted along with the pair-wise test *P-values* for multiple comparisons.

Thus, conducting both trend and pairwise tests complicates the interpretation of the results. Rather than use multiple tests, some members of the Panel recommend that the Agency consider using a single powerful test for a carcinogenic response, namely a trend test. Although the Cochran-Armitage trend test uses a linear dose-response in its definition, it has power to detect all forms of monotone dose-response. Consequently, when this test is significant, it does not imply that the dose-response is necessarily linear.

A standard Cochran-Armitage trend test could lack power if the observed dose response is non-monotone, as might occur when the highest dose exceeds the maximum tolerated dose (MTD) and causes animals to die prematurely. However, this situation can be allayed by using an age-adjusted trend test, e.g., the poly-3 version of the Cochran-Armitage test.

Finally, logistic, probit, or other linear and non-linear regression methods are more powerful than Cochran-Armitage, but depend on a variety of parametric assumptions. Regression methods offer a simple interpretation as a dose-response. Finally, the Panel encouraged the EPA to explore random effects meta-analysis models and generalized linear models to incorporate multivariate effects of gender, species, and strain to help address multiplicity and increase the power of their findings.

The Panel also had comments on the broad issue of statistical evaluation of pairwise comparisons. Overall, some members of the Panel believe that the EPA over-weighted pairwise comparisons in the Issue Paper. Pairwise comparisons have much lower power than tests for trends. Many published studies in nutrition or epidemiology, for examples, also compare the highest and lowest quartiles, looking for differences in extremes. There are methods to improve on power but they suffer from (1) ignoring much of the data and (2) lack of interpretation.

Finally, the Panel made some comments regarding the issue of multiplicity of statistical tests. The Sidak correction for multiple comparisons is available in SAS routines. It assumes independence. Another widely used correction is due to Bonferroni. For very small *P-values*, the Bonferroni and Sidak provide very similar corrected *P-values*. Sidak is slightly less stringent, i.e. the Bonferroni adjustment will find fewer statistically significant results. The Sidak adjustment is not appropriate when multiple comparisons are not independent, such as when several different groups at different exposures are compared to the same control group. There is also the Dunnett test where the pairwise comparisons of interest are comparisons with a control.

The Benjamini-Hochberg (1995) correction is current state-of-the-art for addressing multiple comparisons and is most generous. This procedure is used in the pharmaceutical industry where the incentive is to identify beneficial properties of new formulations by rejecting the null hypothesis as often as possible and still maintain a constant family-wise error rate.

One Panel member provided a specific numerical example to describe how the statistical analyses are performed. A given set of tables such as the September 9, 2016 memorandum: "Updated Statistics Performed on Animal Carcinogenic Study Data for Glyphosate" gives raw and Sidek-adjusted *P-values* (EPA, 2016b; EPA-HQ-OPP-2016-0385-0095). This is the first pair of tables in the document.

The data taken from Lankas (1981) describes an experiment in which 50 rats each were exposed to one of three different levels of glyphosate added to their diet, including 50 rats given an unexposed diet. All 200 were examined by a pathologist for tumors. Much of the Lankas report was concerned with how much each animal ate as a means of describing the total lifetime exposure. These data and the following statistical analysis were also part of the presentation made by Dr. Dunbar (EPA) on Tuesday, 13 December 2016.

Table 2: Lankas, 1981 (MRID 00093879) - rat Testicular interstitial tumors – males and Corresponding Data Analysis

Exposure	0	3.05	10.3	31.49	Total
No tumor	50	47	49	44	190
Tumor	0 (0%)	3 (6%)	1 (2%)	6 (12%)	10(5%)
Total	50	50	50	50	200

Corresponding data analysis:

Comparison	Test	Raw P-value	Sidak P-value
Four groups	Cochrane-Armitage	0.009	Same
0 to 3.05	Fisher Exact (one tail)	0.121	0.321
0 to 10.3	Fisher Exact (one tail)	0.500	0.875
0 to 31.49	Fisher Exact (one tail)	0.013	0.039

The Cochran-Armitage test compares all four exposure levels and tests for a trend in tumor rates. There is only one Cochrane-Armitage test so there is no adjustment for multiple comparisons. The Fisher exact tests construct three 2x2 tables of frequencies comparing each level of exposure to the unexposed, controls.

In this example, the non-parametric Cochran-Armitage test detects a trend, but only the most extreme of the pair-wise comparisons is statistically significant. The Sidak adjusted P-value corrects for the three pair-wise comparisons.

The three Fisher tests are not independent. Each compares the exposed rats to the same control so the Sidak correction is not valid. The Cochran-Armitage test is also correlated to the three Fisher tests so perhaps there should be an adjustment here for four tests, not three.

The original reference, Lankas (1981), points out the elevated tumor rates given in the table illustrated here and states this several times in their introduction. The pathology report begins on stamped page 2841. There were also female rats in this experiment. All animals were examined for tumors in other body organs under a microscope by a pathologist. Several other indications of tumors were identified but explained. The report lists 32 hematology parameters; 8 organ weights; 38 microscopic examinations for 78 total measurements. Then there were two sexes, 3 doses compared to controls, and an overall trend test for a total of (2 sexes by 3 comparisons by 78 measures + 2 sexes x 78 measures x 1 trend test for a total of) 624 potential tests with associated *P-values*. If we were to restrict our attention to only the 78 trend tests in the Lankas (1981) table, one per measure for one species by sex, and performed each test at the typical type I error rate of 0.05, the chance of making at least one false positive conclusion would be 1-(1-

$0.05)^{77} = 0.98$ – a near certainty. Even if we used instead a much stricter individual comparison type I error significance –value of say 0.009, the chance of making at least one false positive conclusion would be 0.5 (a 1 in 2 chance of saying a comparison is statistically different when in fact they were not).

Not all Panel members agreed that multiple comparisons adjustments should be done to determine the carcinogenic potential of glyphosate or that if done these multiple comparisons should combine all cancer endpoints. Regardless, the number of comparisons is relevant when correcting for multiplicity.

Some Panel members suggested that while not discussed in EPA's (2005) *Cancer Guidelines* as to how it considers the multiple studies for each endpoint, the most appropriate way to address the scientific question at hand -- is there evidence of carcinogenic potential in any endpoint in any species or gender? -- is by conducting a pooled analysis for each species, endpoint, and gender combination. A meta-analysis, such as a random effects meta-analysis, is one possible approach to a pooled analysis. An example for three endpoints in mice, for most of the same studies considered by EPA, was provided in the public comments contributed by Dr. Christopher Portier [EPA-HQ-OPP-2016-0385-0449] and his table is reproduced in this report to demonstrate that the pooled analyses he conducted suggest that there is a carcinogenic potential for some cancer endpoints in at least one animal species. This analysis suggests that EPA's descriptor of "suggestive evidence of carcinogenic potential" is the appropriate descriptor, given that these pooled analyses show compelling statistical evidence of at least one single positive result in at least one species and gender. These Panelists recommend that EPA adopt a pooled analysis approach for combining multiple studies. Adopting a pooled analysis approach should include the development of full guidelines for how to conduct and evaluate these analyses.

Table 3: Meta-analysis as one possible approach to a pooled analysis - Example Provided in public comments contributed by Dr. Christopher Portier [EPA-HQ-OPP-2016-0385-0449]

Study	Tumor	Chi-Squared Test		Exact Test		Historical Control Test		Historical
		Original	Poly-3	Original	Poly-3	Original	Poly-3	Control
Knezevich and Hogan, 1983	Renal Tumors	0.033	0.033	0.053	0.055	0.009	0.009	
Atkinson, 1993b		0.94	0.937	0.982	0.982	1	1	
Sugimoto, 1997		0.008	0.009	0.061	0.055	0.009	0.002	
Kumar, 2001		0.04	0.044	0.059	0.06	0.011	0.003	
Wood et al., 2009b		0.5	0.5	1	1	0.629	0.797	11/2939
All experiments combined		<0.001	0.001	0.003	0.003	0.004	0.007	
All CD-1 Studies Combined		<0.001	0.001	0.005	0.006	0.008	0.008	
All experiments combined, doses<1500		0.212	0.207	0.209	0.206	0.206	0.193	
All CD-1 experiments combined, doses<1000		0.851	0.859	0.856	0.853	0.867	0.906	
Knezevich and Hogan, 1983	Malignant Lymphomas	0.515	0.515	0.736	0.731	0.484	0.478	
Atkinson, 1993b		0.076	0.076	0.095	0.096	0.087	0.083	
Sugimoto, 1997		0.008	0.012	0.02	0.018	0.013	0.027	
Kumar, 2001		0.053	0.094	0.105	0.105	0.072	0.106	
Wood et al., 2009b		0.004	0.005	0.008	0.008	0.007	0.008	132/2935
All experiments combined		0.173	0.193	0.476	0.474	0.172	0.199	
All CD-1 Studies Combined		0.015	0.013	0.084	0.089	0.021	0.023	
All experiments combined, doses<1500		<0.001	<0.001	0.002	0.002	0.001	0.001	
All CD-1 experiments combined, doses<1000		0.031	0.045	0.036	0.036	0.039	0.053	
Knezevich and Hogan, 1983	Hemangiosarcomas	0.628	0.628	0.5	0.504	0.592	0.587	
Atkinson, 1993b		<0.001	<0.001	0.004	0.004	<0.001	<0.001	
Sugimoto, 1997		0.008	0.009	0.061	0.051	0.021	0.01	
Kumar, 2001		0.724	0.724	0.494	0.5	0.621	0.713	
Wood et al., 2009b		0.5	0.5	1	1	0.49	0.61	29/2935
All experiments combined		0.041	0.067	0.056	0.058	0.06	0.08	
All CD-1 Studies Combined		0.024	0.03	0.046	0.047	0.04	0.052	
All experiments combined, doses<1500		0.008	0.006	0.016	0.016	0.015	0.012	
All CD-1 experiments combined, doses<1000		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

p<0.01
p<0.05
0.05<p<0.10

c. Unusually low incidences in concurrent controls in comparison with historical controls were noted in Lankas (1981), Stout and Ruecker (1990), and Wood et al. (2009b) and considered as part of the weight-of-evidence for tumor findings. Please comment on the agency's use and interpretation of historical control data as a line of evidence to inform the statistical and biological significance of tumor findings for glyphosate.

Panel Response

Panel comments addressing EPA's use of historical controls vis. a vis. EPA's 2005 Guidelines for Utilizing Historical Control Information

EPA's *Guidelines* for use of historical control data state:

"The standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals."

The Panel suggests that this guideline implies that an analysis based on current controls only should normally take precedence over analyses that incorporate historical control data. The *Guidelines* also state:

"Historical control data can add to the analysis, particularly by enabling identification of uncommon tumor types or high spontaneous incidence of a tumor in a given animal strain."

However, the Panel noted that in none of the three studies in which the Issue Paper reports using historical control incidence rates to down-weigh other analysis results were any of these conditions operative. The EPA *Cancer Guidelines* caution against this use of historical control data:

"Generally speaking, statistically significant increases in tumors should not be discounted simply … because incidence rates in the concurrent controls are somewhat lower than average."

The Panel recommends that EPA clearly explain why historical control rates were used in some analyses and not in others. To subjectively choose to use historical control incidence data only in situations where concurrent control incidence levels are low is to potentially introduce biases.

EPA (2016a) considered historical controls in connection with three tumor responses in three studies: testicular interstitial cell tumors in male Sprague-Dawley rats (Lankas, 1981), pancreatic islet cell tumors in male Sprague-Dawley rats (Stout and Ruecker, 1990) and malignant lymphomas in male CD-1 mice (Wood et al., 2009b).

Regarding the induction of pancreatic islet cell adenomas in male Sprague-Dawley rats [Stout and Ruecker, 1990, MRID 41643801] the Issue Paper concludes that the significant tumor response trend was not treatment-related, in part, because the response in concurrent controls was near the lower bound of the historical range. In fact, the control (2.3%) is within the reported historical range (1.8% – 8.3%), while all three treatment groups had a tumor incidence greater than the upper range for the historical control (10% - 18%). Consideration of historical controls

in this case, instead of being used to down-weigh the result, should be used to add to the weight-of-evidence that this is a significant tumor response.

In the response of testicular interstitial cell tumors in male Sprague-Dawley rats [Lankas, 1981, MRID 00093879], the response in concurrent controls was low compared to the range in historical controls (0% versus a historical control range of 3.4% - 6.7%, average 4.5%). The Issue Paper states "Furthermore, the observed incidence of interstitial cell tumors in the glyphosate-treated groups were within the normal biological variation for this tumor type in this strain of rat." The Panel noted that the incidence in the high dose group was 12%, nearly twice the upper bound for historical controls and hence in this case, the historical control data should again add to the weight-of-evidence that this is a significant tumor response.

In the response of malignant lymphomas in male CD-1 mice in Wood (2009b), it is not clear that the difference in the observed concurrent control group incidence (0%) should be considered unusually low, compared to the cited lower bound among historical controls (1.5%).

EPA's (2005) *Cancer Guidelines* mandate careful review of the historical control data to ensure that it is comparable to concurrent data:

"When historical control data are used, the discussion should address several issues that affect comparability of historical and concurrent control data, such as genetic drift in the laboratory strains, differences in pathology examination at different times and in different laboratories (e.g., in criteria for evaluating lesions; variations in the techniques for the preparation or reading of tissue samples among laboratories), and comparability of animals from different suppliers. The most relevant historical data come from the same laboratory and the same supplier and are gathered within two or three years one way or the other of the study under review; other data should be used only with extreme caution."

The importance of using only historical controls from studies conducted closely in time to when the study being evaluated was conducted was highlighted by a discussion one of the Panel members recently had with a breeder with one of the national labs that supplies a large number of rats and mice for these kinds of studies. The breeder pointed out that despite every effort to keep the characteristics of the animals provided as consistent as possible through careful breeding, the genetics of the population drift over time and hence spontaneous cancer rates drift as well. Their conclusion is that the animal breeding populations "drift" much more and faster than human populations do, given the number of generations that can occur over a year of breeding. Therefore, historical control data that is more than three to five years old may not be representative of the animals currently being supplied.

The *Guidelines* also state that:

"Caution should be exercised in simply looking at the ranges of historical responses, because the range ignores differences in survival of animals among studies and is related to the number of studies in the database."

There is no evidence in the Issue Paper that such a careful review was carried out in any of the three studies that utilized historical control information. In the case of Lankas (1981), the Issue Paper reports only the mean and a range for historical control responses that were provided

in the Lankas study report. There is no information on when or where the data/studies were performed from which these historical control values were calculated, hence the relevance of the historical controls is unknown.

In the case of Stout and Ruecker (1990), the Issue Paper provides historical control rates from the same laboratory for seven years (1983 – 1989), apparently from one study for each year. However, there is no indication of the year in which the Stout and Ruecker (1990) study was completed, which raises the possibility that the recommended range of two or three years for historical controls was not met. Also, the historical data reported suggest that control animals that were scheduled for early euthanasia were included, which could have accounted for the lower historical range observed in this study.

In the case of Wood et al. (2009b), the historical control data did not come from the laboratory that performed the study, but from three different laboratories: 59 studies performed during 1987-2000 from two laboratories and 20 studies performed during 1990-2002 from a third laboratory. There is no discussion of whether the procedures used in these laboratories are compatible with those used in Wood et al., which raises the possibility of non-comparability due to different diagnostic criteria, different methods for preparing and reading tissue samples, different times on test, etc. The year of completion of the Wood et al. study is not mentioned, but it appeared to the Panel that the recommendation that only controls from studies completed within the range of two or three years of the completion of Wood et al. could not have been met.

Summary of Evaluation of Agreement of EPA Analysis with EPA Cancer Guidelines

Overall, based on the previous discussion, many Panelists concluded that the use of historical control information in the Issue Paper does not adhere to EPA *Cancer Guidelines*. There is no evidence that the Issue Paper authors performed a careful review of any of the historical control data employed as directed by the EPA *Guidelines* such as discussing the likelihood of genetic drift, differences among animals from different suppliers, differences in laboratory techniques employed in different studies, etc. The timing of studies from which historical control data came is not always clearly stated, although it is clear that the 2 or 3-year limit recommended in the EPA *Guidelines* was not met in some instances. In some cases, the interpretation of results from applying historical controls is questionable. In none of the applications of historical controls was any attempt made to control for survival in the historical controls or even to determine if the survival of the historical controls was compatible with that of the concurrent animals.

Recommendation on EPA Guidelines for use of Historical Controls

The EPA *Guidelines* need to provide more definitive and clearer guidance on when it is appropriate to use historical control information. As currently written the *Guidelines* seem to offer conflicting information, stating "Historical control data can add to the analysis" along with "the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals" and "statistically significant increases in tumors should not be discounted … because incidence rates in the concurrent controls are somewhat lower than average." A Panel member questioned what the *Guidelines* mean when they recommend using some historical control data only with extreme

caution" or that "caution be exercised in simply looking at ranges…" In addition, it does not quantify what constitutes "unusually low" concurrent control incidence compared to historical control incidence, or whether some statistical test should be used to support this label.

A recent publication discussing the use of historical controls for assessing treatment effects in clinical trials (Viele et al. 2014) offers six methods of incorporating historical control data into testing for treatment effects ranging from ignoring historical data to incorporation of the data using a hierarchical model. Some Panelists recommended that EPA review these and consider adding one or more of these formal methods to its evaluation in the Issue Paper.

Other comments

The EPA document states, drawing from Haseman (1995), that "caution is taken when interpreting results that have marginal statistical significance or in which incidence rates in concurrent controls are unusually low in comparison with historical controls since there may be an artificial inflation of the differences between concurrent controls and treated groups." If this is the case, the significance of comparisons to concurrent controls is still valid. Unusually low control group responses might indicate that this batch of animals are unusually robust, suggesting that they may be unusually resistant to treatment effects. The way the document is written suggests that only the controls are unusually low in comparison to the treatment groups, but if true randomization is used the "unusualness" must apply to the whole batch of animals used.

One Panelist observed that the use of historical controls in the analysis of data can be expressed using Bayesian methods. The Bayesian analysis adds a number of "virtual" animals to the control group and a specified percent of these have tumors. In the analysis of the current data, this is how to express weight to the historical controls.

A member of the Panel also noted that a 2-Acetylaminoflourene (2-AAF) study (Farmer, 1979) used many hundreds of control mice and about 1/3 of 1% of these developed liver cancer. It was suggested that, this information could be used by expressing it as a distribution with corresponding uncertainty or variability in any future study of 2-AAF. Other Panel members felt that too much time has elapsed since this study was conducted for the incidences in controls to be useful in future studies.

Final comment

The Panel agreed with the statement in the EPA *Guidelines* that "The standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals." Given this, the Panel believed that the default position should always be to not use historical control information, and, in those cases when it can be used, there should be a clearly articulated reason. When these conditions are satisfied, the requirement in the 2005 *Guidelines* for careful review of the historical data to ensure that it is comparable to concurrent data should be strictly followed.

d. Please comment on the agency's conclusion that there is an absence of corroborating preneoplastic lesions or related non-neoplastic lesions. Please also comment on the agency's conclusion that there is a lack of progression to malignancy to support tumor findings.

Panel Response

The Panel noted that the Issue Paper does not adequately describe its process for identifying and assessing information on pre- and non-neoplastic lesions. From the documentation provided, it was unclear whether a pre-determined process for identifying significant changes in pre- and non-neoplastic findings was employed and, if so, what criteria were used to select data for statistical analyses. For example, it was not clear what kinds of lesions were important for which cancer endpoints in which sexes or species. Also unclear is how the identification of pre-neoplastic lesions supports or is supported by an assumption of a mechanism of tumor induction.

One Panel member noted that in some instances, due diligence in review of the available information was performed and its process included in the Issue Paper. In these cases, further studies were done that included histopathological examination of laboratory animals during and at the end of long-term experiments. Pre-neoplastic lesions should have been noted in tissues collected at midterm euthanasia as well as in tissues collected at the end of the experiment. Observation of pre-neoplastic lesions is expected when some in a group of test animals have neoplastic lesions at the end. The dearth of such pre-neoplastic lesions during and at the end of the experiments presented decreases the likelihood of time-related toxicant-induced effects.

Most Panel members were in agreement that, overall, there is a paucity of evidence for pre-neoplastic findings defined as hyperplasia. When pre-neoplastic lesions were present, in most cases there was no progression to or congruence with adenomas or carcinomas.

Some members of the Panel noted situations where the information reported in the Issue Paper was different than what was reported in the source documents:

1. There are differences in the numbers in tables in the Issue Paper and those in the source documents both with respect to the incidence and number of animals at sacrifice;

2. High dose effects (i.e., >4,000 ppm or 1,000 mg/kg) are discounted despite a lack of pharmacokinetic and/or pharmacodynamic information for doses at this level.

3. There is an increase in the incidence of commonly occurring tumors in aged animals that is not mentioned in the Issue Paper;

4. There are some pre-neoplastic effects attributed to glyphosate treatment in the source documents that are not cited in the EPA Issue Paper;

Panel members found that pre-neoplastic effects attributed to glyphosate treatment in source documents that are not cited in the Issue Paper include the following:

Rat Studies:

- Lankas, 1981: Lymphocytic hyperplasia increased in the thymus of males (M) and females (F), in the mediastinal lymph node (M), the mesenteric lymph node (F), and the spleen (M), in addition C-cell hyperplasia (F) was observed in the thyroid. Spleen reticulum cell sarcoma was reported in females.

• Atkinson et al. 1993a: The most notable histological finding was seen in the salivary glands, where cellular alteration was seen in the submaxillary and/or parotid of males and females.

• Brammer, 2001: In kidney, slight increased incidence of papillary necrosis was observed in M>F, with varying degrees of mineralization of the papilla and/or transitional cell hyperplasia. In pancreas, exocrine hyperplasia increased in high-dose males (within historical control values).

• Suresh, 1996: In spleen, lymphoid hyperplasia increased in the low dose group. Specifically, lymphoid hyperplasia of the mediastinal lymph nodes increased in the low dose group and increased in the mandibular lymph nodes of low and high dose groups. In liver, clear cell foci/areas increased in low and mid dose groups and were described as "Maybe pre-neoplastic changes as evidenced by the high incidence of hepatic tumors in these animals," in the primary study document.

• Wood et al, 2009a: In kidney, hyperplasia of the pelvic/papillary epithelium was observed in the high dose group. In males, pancreas islet cell hyperplasia (minimal) increased in the mid dose group [2/12, 4/13, 7/13, 0/6] and thyroid C-cell hyperplasia increased in the high dose group.

Mouse Studies:

• Knezevich and Hogan, 1983: In liver of males, focal hyperplasia and testes interstitial cell hyperplasia were observed in the low dose group. In uterus, cystic endometrial hyperplasia was observed.

• Atkinson et al., 1993b: The incidence of lung masses was slightly higher in the high dose group (18/50) compared to control (10/50).

Most Panel members were in agreement that, overall, there is a paucity of evidence for dose-related increases in pre-neoplastic findings co-occurring with increases in adenomas or carcinomas in the same tissue. However, significant lymphoid hyperplasia was observed at low and mid doses in males (71.4 and 234.2 mg/kg/day) in a study where malignant lymphomas were significantly induced at 810 mg/kg/day (Wood, 2009a).

It was noted that two studies identified an inverse relationship between dose and the incidence of pre-neoplastic lesions. In the Atkinson et al. (1993a) study of Sprague-Dawley rats, a significant decrease in kidney hyperplasia was observed in female rats (total incidence score: 18/50, 17/49, 13/50, 9/49, and 1/50 for doses of 0, 10, 100, 300, and 1000 mg/kg-bw/day). In the Knezevich and Hogan (1983) study of CD-1 mice, "There was actually a decrease in renal tubule epithelial changes (basophilia and hyperplasia in males, and although there was a dose-related increase in these changes in females, no tubular neoplasms were observed in females)." Some Panel members concluded that these observations are consistent with the interpretation that glyphosate is non-genotoxic and does not cause *de novo* pre-neoplastic lesions, but rather glyphosate is a weak, non-genotoxic carcinogen that causes outgrowth of pre-existing spontaneous lesions. This interpretation is supported by multiple positive tumor bioassays [significant in individual or combined analyses (see Charge Question 3b), as well as three positive tumor responses observed in a single bioassay], the lack of evidence of genotoxicity,

treatment-related increases in frequently occurring spontaneous tumors (Knezevich and Hogan 1983, Wood 2009b), treatment-related decreases in pre-neoplastic lesions concurrent with increases in tumor frequency within the same organ (Lankas 1981, Knezevich and Hogan, 1983), and significant increases in malignant tumors of treated male rats relative to controls across tumor sites (Atkinson 1993a).

Regarding the Issue Paper's conclusion that there is a lack of progression to malignancy to support tumor findings, one Panel member noted that three different malignancies were significantly induced by glyphosate ($P < 0.01$ for malignant hemangiosarcoma, lung adenocarcinoma, and malignant lymphoma). In addition, the study of glyphosate-treated Sprague-Dawley rats by Atkinson et al. (1993a) stated "the overall number of animals with tumors was similar between groups (44/50 in control vs 41/50 in high dose males: 49/50 in control and high dose females), but the number of males in the high dose group with malignant tumors (15/50 or 30%) was almost double that observed in controls (8/50 or 16%)." The Wood study (2009b) of CD-1 mice reported an overall increase in multiple malignant tumors in treated males relative to controls. For this Panel member, these observations regarding malignancy add to the weight-of-evidence that glyphosate is a rodent carcinogen.

The Panel recommends that the Issue Paper revise and strengthen its discussion on the process used for identifying and assessing information regarding pre- and non-neoplastic lesions. In the process, the Issue Paper should address the exclusions discussed above.

e. In the case of glyphosate, there are multiple carcinogenicity studies available for the evaluation of carcinogenic potential. The agency looked across all of the studies and found that tumor findings were not consistent or reproduced in other studies conducted in the same species and strain at similar or higher doses. Please comment on the interpretation of conflicting evidence and reproducibility for these studies.

Panel Response

The Panel was divided with regard to the interpretation of apparently inconsistent evidence from the rodent bioassays of glyphosate. Some Panel members pointed out that true carcinogenic responses should be reproducible, and that the apparently positive results in some of the rodent bioassays of glyphosate were likely to be false positives. In particular, these Panelists believe that the lack of corroborating information from bioassays using the same or higher doses and in the same rodent species, strain, and sex is important evidence against a genuine carcinogenic effect of glyphosate.

Other Panel members, however, believed that differences in study designs could explain some of the tumor response discrepancies, and that, overall, the rodent bioassay data were consistent with glyphosate acting as a weak tumor promoter. As mentioned in response to question 3b, a pooled analysis that appropriately addresses differences in study design is recommended by some Panel members to determine whether or not the evidence from multiple rodent studies is indeed conflicting.

There has been no direct test of the weak promoter hypothesis (such as in a standard initiation-promotion bioassay), and some Panel members felt that such a conclusion was

speculative. Nonetheless, some of the high-dose responses in some of the fifteen or more bioassays of glyphosate were noteworthy, at least to some Panelists. EPA mentioned that dose-rates of greater than 1,000 mg/kg-day are considered to be above the "limit dose," but, in the case of glyphosate, its remarkable non-toxicity means that it can be reliably applied in bioassays at up to several grams/kg-day. Thus, in these Panelists' opinions, positive results at doses at and above the "limit dose" should not necessarily be discounted. Other Panelists also believe that the limit dose is used as a study design guideline and should not be used to discount findings after a study has been conducted. See further discussion of the appropriateness of the limit dose criterion in response to charge question 3f.

Some Panelists noted that the Issue Paper correctly noted the lack of reproducibility of statistically significant carcinogenic effects in the glyphosate rodent bioassays. However, this was noted only in a single sentence at the end of the discussions of the evidence from rat and mouse data (Section 4.8). These Panelists suggest that it would be helpful to substantiate this point by reviewing the information that led to this conclusion. To this end, these Panelists provide, in the following paragraphs, their summaries of the data from the rodent glyphosate studies available to the Panel on each of the cancer endpoints analyzed in the Issue Paper.

In Table 4.1 of the Issue Paper, the response of testicular interstitial cell tumors (also known as Leydig cell tumors) in male Sprague-Dawley rats (Lankas, 1981) had a significant dose response trend ($P = 0.0062$ by the exact form of Cochran-Armitage trend test (Gart et al. 1986, p. 81-86)). The highest dose in Lankas et al. was only 31 mg/kg/day, and for this reason was given the lowest rating (Klimisch 3) by Greim et al. (2015). Other studies of Sprague-Dawley rats using doses 30-fold higher or greater, from 940 mg/kg/day to in excess of 1000 mg/kg/day (Stout and Ruecker 1990; Atkinson 1983a; Enemoto 1997), did not show statistical evidence of an effect on testicular interstitial cell tumors. Indeed, in all of the 15 rodent bioassays, increases in Leydig cell tumors were seen only once.

In Table 4.2 of the Issue Paper, the response of pancreatic islet cell adenoma in male Sprague-Dawley rats (Stout and Ruecker 1990, high dose $\approx$ 1000 mg/kg/day) was analyzed. Although the trend test was not significant ($P = 0.18$) this analysis was included because of a significant increase at the lowest dose in a pair-wise test before adjusting for multiple comparisons ($P = 0.018$). The trend test for the combined response of adenoma or carcinoma gave a $P = 0.21$, not significant. However, in this same study there was a significant negative trend in female mice for both adenoma ($P = 0.04$, negative trend) and adenoma or carcinoma combined ($P = 0.04$, negative trend). Thus, overall, there appears to be greater evidence for a protective effect on pancreatic islet cell tumors in this study than a carcinogenic effect. However, these results most likely stem from natural variation in tumor responses, rather than any effect of treatment. Atkinson (1983a, high dose $\approx$ 1150 mg/kg/day) found a significant negative trend for this tumor among male Sprague-Dawley rats ($P = 0.007$, negative trend) using doses spanning those in Stout and Ruecker (1990). Enemoto (1997, reported in Greim 2015, high dose $\approx$ 1130 mg/kg/day) exposed male and female Sprague-Dawley rats to doses that spanned those used by Stout and Ruecker (1990) and found no statistical evidence of a dose effect. Also, two studies of male and female Wistar rats found no statistical evidence of a dose effect on pancreatic islet cell adenoma or adenoma and carcinoma (Brammer 2001, high dose $\approx$1300 mg/kg/day; Wood et al. 2009a, high dose $\approx$ 1100 mg/kg/day).

In Table 4.4 of the Issue Paper, hepatocellular adenoma in male Sprague-Dawley rats (Stout and Ruecker 1990, high dose ≈ 1000 mg/kg/day) was shown to have a significant dose response trend ($P = 0.02$), and, as a result, the combined response of hepatocellular adenoma and carcinoma was nearly significant ($P = 0.078$). In this same study there was an almost significant negative trend in hepatocellular adenoma among females ($P = 0.078$, negative trend). Atkinson et al. (1983a, high dose = 1000 mg/kg/day) and Enemoto (1997, as reported in Greim 2015, high dose ≈ 1200 mg/kg/day) also exposed Sprague-Dawley rats to doses that spanned those used by Stout and Ruecker (1990) and found no statistical evidence of a positive dose effect on adenoma or the combination of adenoma or carcinoma. In the Issue Paper, Table 4.9, hepatocellular adenoma in male Wistar rats (Brammer 2001, high dose ≈ 1300 mg/kg/day) had a significant dose response trend ($P = 0.0082$). However, Suresh (1996, high dose = 740 mg/kg/day) and Wood et al. (2009a, high dose ≈ 1300 mg/kg/day) exposed Wistar rats and found no statistical evidence of a positive dose effect, although there was an almost significant negative trend in hepatocellular adenoma for females in Suresh (1996) ($P = 0.08$, negative trend).

In Table 4.7 of the Issue Paper, thyroid C-cell adenoma in female Sprague-Dawley rats (Stout and Ruecker, 1990, high dose ≈ 1000 mg/kg/day) had a significant dose response trend ($P = 0.040$) and the trend in the combined response of adenoma or carcinoma was also significant ($P = 0.042$). The corresponding trends in male Sprague-Dawley rats were almost significant (adenoma response $P = 0.079$ and combined response $P = 0.087$). Atkinson et al. (1983a, high dose ≈ 1000 mg/kg/day) also exposed Sprague-Dawley male and female rats to comparable high doses with no statistical evidence of a dose effect on these tumors. There was a statistically significant trend ($P = 0.0026$) in thyroid C-cell carcinoma among female Sprague-Dawley rats in Lankas et al. (1981, high dose = 34 mg/kg/day), however the high dose in this study was well below the low dose in Stout and Ruecker (1990). Suresh (1996, high dose ≈ 740 mg/kg/day), Brammer (2001, high dose ≈ 1200 mg/kg/day) and Wood et al. (2009a, high dose ≈ 1200 mg/kg/day) exposed Wistar rats and found no statistical evidence of a positive dose effect on C-cell tumors. However, in Wood et al. among female Wistar rats there was a statistically significant negative trend in thyroid C-cell adenoma (recorded as parafollicular adenoma (Greim et al. 2015)) ($P = 0.0030$, negative trend), and a statistically significant negative trend in the combined response of C-cell adenoma or C-cell carcinoma (recorded as parafollicular carcinoma) ($P = 0.0021$, negative trend). Similarly, among male Wistar rats in Wood et al. (2009a) there were almost significant negative trends for thyroid C-cell carcinoma ($P = 0.062$, negative trend) and the combined response of thyroid C-cell adenoma or carcinoma ($P = 0.064$, negative trend).

In Table 4.10 of the Issue Paper, mammary adenocarcinoma in female Sprague-Dawley rats (Wood et al. 2009a, high dose ≈ 1200 mg/kg/day) had a significant dose response trend ($P = 0.042$) and the trend in the combined response of adenoma or adenocarcinoma was also significant ($P = 0.0067$). Brammer (2001, high dose = 1500 mg/kg/day) and Suresh (1996, high dose = 740 mg/kg/day) also exposed female Sprague-Dawley rats and found no statistical evidence of a positive effect on mammary tumors. However, there was a significant negative trend in mammary gland adenocarcinoma among female Sprague-Dawley rats in Suresh (1996 high dose = 741 mg/kg/day) ($P = 0.018$, negative trend).

In Table 4.12 of the Issue Paper, adenoma or carcinoma in tubule cell tumors in male CD-1 mice (Knezevich and Hogan, 1983, high dose ≈ 5000 mg/kg/day) had a non-significant dose-

response trend ($P = 0.065$). None of these tumors were seen in females. Atkinson et al. (1993a, high dose ≈ 1000 mg/kg/day) found two tubule cell adenomas in CD-1 male mice which occurred in control and low dose groups. Wood et al. (2009b, high dose ≈ 900 mg/kg/day) also exposed CD-1 mice, but did not record any incidences of tubule cell tumors.

In Table 4.14 of the Issue Paper, haemangiosarcoma in male CD-1 mice (Atkinson, et al., 1993b, high dose = 1000 mg/kg/day) showed a significant dose-response trend ($P = 0.002$), resulting from a total of four haemangiosarcomas, all appearing in the high dose group. Three haemangiosarcomas were detected in female mice but their distribution in the dose groups did not suggest a dose-response trend. Knezevich and Hogan (1983, high dose ≈ 5000 mg/kg/day) did not report finding any haemangiosarcomas among male or female CD-1 mice. Wood et al. (2009b, high dose ≈ 900 mg/kg/day) reported finding 6 haemangiosarcomas in male CD-1 mice (2 in controls, 1 at the low dose, 2 at the middle dose and 1 at the high dose) and four haemangiosarcomas in female mice (1 in each dose group).

In Table 4.15 of the Issue Paper, the incidences of lung tumors are recorded for male CD-1 mice (Wood et al. 2009b, high dose ≈ 900 mg/kg/day). A significant trend is reported for adenocarcinoma ($P = 0.028$), but not for adenoma or the combination of adenoma and adenocarcinoma. There is an almost significant negative trend for adenoma ($P = 0.078$, negative trend). Knezevich and Hogan (1983, high dose ≈ 5000 mg/kg/day) found a highly significant negative trend for adenoma in female CD-1 mice ($P = 0.00058$, negative trend) and a significant negative trend for the combination of adenoma and adenocarcinoma ($P = 0.015$, negative trend). They also found a near significant negative trend for adenocarcinoma in male mice ($P = 0.094$, negative trend). Neither Atkinson et al. (1993b, high dose = 1000 mg/kg/day) nor Sugimoto (1997, high dose ≈ 4200 mg/kg/day) found statistical evidence for an effect on lung tumors in either male or female CD-1 mice.

In Table 4.16, of the Issue Paper, malignant lymphomas in male CD-1 mice (Wood et al., 2009b, high dose ≈ 900 mg/kg/day) had a significant dose response trend ($P = 0.0066$). Sugimoto (1997, high dose ≈ 4200 mg/kg/day) also found a significant trend ($P = 0.016$) for malignant lymphoma in male CD-1 mice. However, the two responses do not appear congruent: Wood et al. found a significant excess (5/51) at a dose of 810 mg/kg/day, whereas Sugimoto found no tumors (0/50) at a comparable dose (838 mg/kg/day). Knezevich and Hogan (1983, high dose ≈ 5000 mg/kg/day) found an almost significant trend in malignant lymphoma ($P = 0.063$) among female CD-1 mice, but there was no evidence of a positive trend in males (equal responses of 2 animals in both the highest dose group (4841 mg/kg/day) and in controls).

In Table 4.17 of the Issue Paper, haemangiomas in female CD-1 mice (Sugimoto 1997, high dose ≈ 4100 mg/kg/day) showed a significant dose-response trend ($P = 0.0022$). (This study was not available to the Panel.) Neither Knezevich and Hogan (1983, high dose ≈ 5000 mg/kg/day) nor Wood et al. (2009b, high dose ≈ 900 mg/kg/day) found any statistical evidence for an effect of treatment on the incidence of haemangiomas in either CD-1 male or female mice.

The Panel observed that an explanation needs to be provided in the Issue Paper of the criteria used to select tumors for detailed evaluation. Was a well-defined tumor selection procedure used (such as a minimum number of total tumors), or was it based on the original authors' evaluations?

Following this assessment, some Panelists concluded that the Issue Paper correctly finds the tumor-response data to be too inconsistent to be credibly considered to be compound-related. In many cases there were significant or near significant negative trends in the same tumor categories as those in which significant positive trends were identified. As noted elsewhere, with so many tumor categories recorded in these studies, a few significantly positive trends (and significantly negative trends) would be expected in each study even if the treatment has no effect on tumor rates. This multiple comparison problem is particularly acute in the case of glyphosate, because of the exceptionally large number of rodent studies available. This conclusion is consistent with the assessment presented by Dr. Haseman before the Panel, which showed the number of significant trends (at both significance levels of 0.05 and 0.01) in the animal study data are no greater than what would be expected simply due to the random assignment of animals to dose groups without any carcinogenic effect of glyphosate exposure.

Other Panelists pointed out that the Issue Paper ascribes equal weight to the 15 acceptable rodent carcinogenicity studies and concludes that "tumors seen in individual [rat or mouse] studies were not reproduced in other studies conducted in the same animal species and strain at similar or higher doses." These Panelists noted that in order to judge whether this conclusion is valid (and should be given more weight than the positive tumor findings), one must consider whether the studies were of similar quality, employed rodents with equivalent tumor sensitivities, and whether equivalent tumor incidence data was analyzed in a consistent manner. The Panel collected data from the primary study documents that suggests the studies varied with respect to these criteria. Some observations about how these studies varied in meaningful ways that could affect direct comparability, such as the direct comparisons made above, are provided in the following paragraphs.

The studies varied in terms of design and quality, in ways expected to impact their sensitivity. For example, the study by Lankas (1981) [MRID 00093879] treated rats for 26 months, which may explain why it detected a tumor response not detected in the other studies that treated rats for 24 months. The Stout and Ruecker (1990) rat study generated statistically significant responses for three different tumor types. This study may have had greater sensitivity than others because it employed 60 rats/treatment group (the largest number of rodents in any glyphosate study). In this regard, it should be noted that the glyphosate Issue Paper statement "...tumors at multiple sites..." is an observation that adds strength to the significance of tumor findings in carcinogenicity studies.

Across the mouse studies, mice were exposed through the diet for between 16 to 24 months. The mouse study by Reyna and Gordon (1973) sacrificed males after 16 months, females after 18 months and included histopathological analyses on only 10 mice per dose. Clearly, this study should not be weighted as heavily as studies where histopathology results were obtained from all 50 animals/sex/dose.

Some of the studies had low survival at terminal euthanizing (<20 animals/group), which is expected to reduce the sensitivity of the bioassay.

The study by Pavkov and Wyand (1987) [MRIDs: 40214007, 41209905, and 41209907] used a distinct test article and vehicle (Sulfonate, glyphosate trimesium salt and a 1% propylene glycol vehicle). The mouse bioassay by Pavkov and Turnier (1987) [MRIDs: 40214006 and

41209907] also employed Sulfonate as the test article and propylene glycol as the vehicle. It is inappropriate to consider a study as a reproduction of another study if a different test article was used.

In the Pavkov and Turnier study, males in the 0 ppm treatment group were euthanized after 89 weeks of treatment, whereas mice in the other treatment groups were euthanized after 95 weeks of treatment.

It was not clear to the Panel how tumor responses were systematically examined and reported by research pathologists across studies. For the majority of the studies presented in the Issue Paper, the combined incidence of euthanized in extremis/found dead plus terminally-euthanized animals were used in the analyses. In some cases, the Issue Paper assessment excluded animals that died before 55 weeks, but in other cases the use exclusion/inclusion status of these animals is unknown. For example, the Pavkov and Wyand and Pavkov and Turnier studies combined data on interim euthanized (6, 12, and 18 months) with moribund/dead and euthanized post experimental termination for statistical analysis. For Stout and Ruecker, the data are broken out as scheduled euthanizing (12 and 24 months?), unscheduled deaths, and "all deaths reported." The Panel found it was unclear from reading the Issue Paper whether analysts were able to parse out and analyze equivalent datasets using the same statistical approach for all 15 rodent carcinogenicity datasets. The Panel recommends the Issue Paper adds a section with a detailed description of which data were extracted and precisely how data were selected for subsequent analysis.

The Panel found no discussion in the Issue Paper of the extent to which histopathological examinations were performed in an equivalent manner across studies. The rat bioassay by Suresh (1996) [MRID 49987401] did not include histopathological analyses on all the low and mid-dose rats at terminal euthanizing and reported that "autolysis precludes evaluation" of many samples.

The Panel noted that it is also important to consider genetic variability across rodent strains used and how this variability impacts bioassay reproducibility.

Rodent strains maintained as separate breeding colonies for extended periods of time do not necessarily have the same spontaneous tumor profiles (King-Herbert and Thayer, 2006). This is the basis for the OECD recommendation that only studies performed within five years in the same laboratory should be considered as historical controls. To evaluate the variability among the rodents used, the incidence of a single tumor type in control rodents was compared across glyphosate studies.

- Male Sprague-Dawley rats, pituitary tumor rates reported as 40%, 56.6%, 58%, 70% and 52%.
- Female Sprague-Dawley rats, pituitary tumors rates reported as 88%, 76.7%, 81.6%, 94%, and 72%.
- Male Wistar rats, pituitary tumor rates reported as 30%, 34%, and 6%.
- Female Wistar rats, pituitary tumors rates reported as 80%, 47%, and 16%.

- Male CD-1 mice, pituitary tumors rates reported as 64%, 0%, 0%, and 0%.

- Female CD-1 mice, pituitary tumors rates reported as 64%, 2%, 0%, and 0%.

These data suggest that even within a particular rodent species there are relatively large differences in background tumor incidence rates which might be expected to impact the detection of statistically-significant findings.

Reported toxicological findings also varied across the different tumor bioassays, providing additional evidence of biological and/or methodological variability in the studies conducted in the US, the UK, Japan, and India between 1973 and 2009.

Most importantly, before one can conclude that the findings in individual studies are not replicated, one must compare the results across studies in a rigorous manner. Similar patterns of tumor responses were observed across studies for some tumor types.

- Lung: six studies in which all glyphosate treated groups have an equal or greater tumor incidence than the concurrent control group (for at least one tumor type in one sex), with the highest observed tumor incidence approximately twice the control level.

- Liver: five studies in which all glyphosate treated groups have an equal or greater tumor incidence than the respective control group (for at least one type of tumor in one sex) and the highest observed tumor incidence is approximately twice the control level.

- Lymphatic and thyroid tumors: three studies in which all glyphosate treated groups have an equal or greater tumor incidence than the respective control group (for at least one type of tumor in one sex) and the highest observed tumor incidence is approximately twice the control level.

One Panel member was of the opinion that this constitutes reproducible evidence of a biologically-significant carcinogenic effect in rodent liver, lung, thyroid, and lymphoid cells.

f. As described in Section 1.4, high-end estimates of exposure based on the currently registered uses for glyphosate in the United States have been calculated as 0.47 mg/kg/day and 7 mg/kg/day for potential residential and occupational exposures, respectively. As a result, the agency concluded that tumors observed at high-doses (approaching or exceeding 1,000 mg/kg/day) following glyphosate administration are not relevant for human health risk assessment. Please comment on the conclusions regarding the relevance of high-dose tumors to the human health risk assessment for glyphosate.

Panel Response

The EPA (2016a) evaluation defined 1,000 mg/kg/day as the "limit dose" and high-dose tumors (e.g., tumors in animals exposed to greater than 1,000 mg/kg/day) were given less weight. All but five of the 15 rodent studies investigated involved doses that exceeded 1,000

mg/kg/day. However, the EPA (2005) *Cancer Guidelines* suggest that an excessively high dose would be "5% of the test substance in the feed for dietary studies." None of the 15 studies utilized a dose as high as 5%. The highest tested dose in any of the 15 studies appears to be 30,000 ppm (3%) in the Knezevich and Hogan (1983) CD-1 mouse study. Therefore, at least based on EPA (2005) *Cancer Guidelines*, some members of the Panel concluded it is questionable whether results from exposures greater than 1,000 mg/kg/day, but less than doses corresponding to 5% in diet, should be given less weight. Disregarding responses at any dose above a pre-selected "limit dose," even though the dose did not exceed the maximum tolerated dose (MTD), is not in keeping with the way rodent bioassays are normally interpreted, which is to answer the question "was the test material carcinogenic in this study (assuming that the study did not use doses that exceeded the MTD)." Thus selecting 1,000 mg/kg/day *a priori* as the limit dose appears to be an *ad hoc* decision that is not well-justified, and is not justified on the basis of the EPA (2005) *Cancer Guidelines*.

One Panel member noted the possibility whereby a carcinogenic response at 1,000 mg/kg/day could, depending on the dose-response shape at lower doses, translate into an estimated human risk as high as 1% from a lifetime exposure to 7 mg/kg/day, the stated maximum potential exposure level for occupational exposure (assuming a 10% risk at 1,000 mg/kg/day in a mouse bioassay, a linear dose-response to lower doses, and using a surface area conversion from mice to humans, which entails multiplying by roughly a factor of 13). Further, a carcinogenic effect at a dose >1,000 mg/kg/day could suggest a carcinogenic effect is also occurring at lower doses, which cannot be detected due to lack of power.

The Panel concluded that the Issue Paper needs to clarify its position on results from exposures that exceed 1,000 mg/kg/day. In at least one place the document says that the tumor responses, including those from doses exceeding 1,000 mg/kg/day, are not related to treatment. For example, "in 5 of the 9 rat studies conducted with glyphosate, no tumors were identified for detailed evaluation. Of the remaining 4 rat studies, a statistically significant trend was observed for tumor incidences in the testes, pancreas, liver, thyroid, or mammary gland; however, the agency determined that these tumor findings are not considered to be related to treatment…." The statistically significant trends discussed in this paragraph are based on data at all the doses, including those exceeding 1,000 mg/kg/day. Thus, this paragraph indicates that the Issue Paper does not consider the tumor responses at any dose, including those exceeding 1,000 mg/kg/day, to be related to treatment. On the other hand, there are numerous statements in the report that suggest that tumors occurring at doses exceeding 1,000 mg/kg/day are related to dose:

"…tumor incidence in animal carcinogenicity studies was typically only increased at the highest doses tested (≥1,000 mg/kg/day)."

"… however, the data are not sufficient to determine whether linear kinetics is occurring at high doses where tumors were observed in animal carcinogenicity studies."

"Tumor incidences were not increased in animal carcinogenicity at doses <500 mg/kg/day, …"

"In the remaining studies, tumor incidences were not increased at doses <500 mg/kg/day, except for the testicular tumors observed in a single study. Increased tumor incidences at or exceeding the limit dose (≥1000 mg/kg/day) are not considered."

"even though tumors were observed in animal carcinogenicity studies, the possibility of being exposed to these excessive dietary doses …"

The Panel found that these statements suggest that the Issue Paper considers some tumors occurring at >1,000 mg/kg/day to be related to dose.

Many on the Panel expressed concern that not considering tumor responses at doses exceeding 1,000/mg/kg/day is not consistent with either EPA (2005) *Cancer Guidelines* or standard ways in which bioassay results are typically interpreted. However, the Panel also noted that tumors induced at only very high doses are less of a safety concern than those induced at doses within the range of human exposure; though one Panel member noted that it is very likely that workers in manufacturing/formulation and wholesale handling and also persons involved in accidents and spills may experience these high exposures.

There were some differences of opinion among Panel members regarding the relevance and use of high-dose tumors for human health risk assessment of glyphosate. Some Panel members felt that at high doses homeostatic mechanisms can be overwhelmed (e.g., the saturation of elimination processes) and, hence, allowances need to be made in the interpretation of high dose data. Other Panelists felt that data from high doses should be included with a caveat that high doses could lead to toxicity, but not carcinogenicity. Still other Panelists felt that if there were tumors in the presence of other toxicity at high doses, that would be cause for concern regarding the interpretation of the results and potentially justification for excluding the data.

One Panel member noted that effects consistent with carcinogenic potential occurred at doses lower than 1,000 mg/kg/day. Specifically, significant induction of lymphocytic hyperplasia was observed at 11 mg/kg/day (Lankas, 1981). Significant lymphoid hyperplasia was observed at low and mid doses in males (71.4 and 234.2 mg/kg/day) in a study where malignant lymphomas were significantly induced at 810 mg/kg/day (Wood, 2009a). Male Sprague-Dawley rats in the Lankas study (1981) demonstrated a significant trend and a significant pairwise comparison between control and the high dose for testicular interstitial tumors, when the high dose was 31.49 mg/kg/day. A significant pairwise comparison relative to controls was observed for pancreatic islet cell tumors in male Sprague-Dawley rats at the low dose, 89 mg/kg-bw/day (Stout and Ruecker, 1990). In the view of one Panel member, these carcinogenic effects in rodents should be considered when setting acceptable levels of glyphosate exposure.

As a general matter, EPA usually does not consider tumors observed at high doses in rodent bioassays to be necessarily irrelevant for purposes of human cancer risk assessment. However, if these observations are in fact false positives, then discounting them would indeed be appropriate. Making a *post hoc* assessment to discount high doses after the studies were designed and carried out using existing guidelines poses a concern.

The Panel noted that one bioassay did report a positive result (for Leydig cell tumors in a group of Sprague-Dawley rats) at a glyphosate-dose of only 31 mg/kg/day. However, some Panel

members noted that Leydig cell tumors (i) are quite common in Sprague-Dawley rats, (ii) are very difficult to distinguish from simple hyperplasia, and (iii) were not found to be associated with glyphosate in any of the other 14 bioassays, including those that used the same species, strain, and sex -- even at doses at and above 1,000 mg/kg-day.

One Panel member also noted that glyphosate acid (the form used in the bioassays) has a pH of 2 at saturation, so that very high-dose responses might be due to simple acidity, rather than to a compound-specific effect. Since glyphosate as used in commerce is not an acid but instead a more neutral salt or zwitterion, such effects might well be irrelevant for purposes of human cancer risk assessment.

g. Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available animal carcinogenicity studies, as described in Section 4.8.

Panel Response

Some Panelists felt that the Issue Paper did a good job discussing strengths and uncertainties of the animal carcinogenicity studies whereas others disagreed with the interpretation of the rodent carcinogenicity data as presented in EPA's Issue Paper. Responses to the previous sub-questions of Charge Question 3 give detailed discussion of the Panel's view of the considerations that went into the weight-of-evidence analysis.

The Panel members who disagreed with the Agency's interpretation of the rodent carcinogenicity data felt that the EPA (2016a) weight-of-evidence evaluation gave excessive weight to several factors: monotonic dose responses, historical tumor rates, lack of statistical significance in pair-wise comparisons when there is a significant trend, and disregarding or giving low weight to results at exposures > 1000 mg/kg/day.

Most Panelists were in general agreement that EPA's weight-of-evidence did not properly address the unusually large number of bioassays available for glyphosate. Some Panelists concluded that EPA ignored the serious multiple comparison problem caused by focusing attention on the most extreme tumor responses out of a large number of responses. Some Panelists determined that the best way to address this concern was to conduct properly pooled analyses, in order to determine the most conclusive answer to the question of whether there was evidence of a carcinogenic effect in any cancer endpoint, in any species or gender. See the extensive discussion of the Panel's thoughts on how to address the unusually large number of bioassays in response to Charge Question 3b.

Still other panelists, while agreeing that pooling can have the beneficial effect of allowing results in the same cancer endpoint from different sets of data to reinforce one another, pooling does not address the multiple comparison problem *per se*. In a large data set such as exists for glyphosate there will be a large number of responses that can be pooled, and consequently the multiple comparison problem will remain. This problem can be addressed by applying statistical tests specifically designed for tumor bioassay data that provide a single valid P-value for a tumorigenic effect at any site, which can also be designed to allow results in the same cancer endpoint from different sets of data to reinforce one another.

Each of the considerations for the weight-of-evidence analysis called out above are summarized briefly in the remainder of this response. See previous Charge Question responses for additional details.

Monotonicity

The Panel noted that the fact that an observed dose-response is not monotone typically provides essentially no evidence that the underlying true dose response is non-monotone. Furthermore, checking for monotonicity is not mentioned in EPA (2005) *Cancer Guidelines*. In the simulated examples reported earlier the probability of a non-monotone was 0.57 and 0.70 even though the true dose responses were monotone increasing or non-decreasing.

Historical Control Rates

In cases in which the Issue Paper incorporated historical control rates in setting weights, it was used to down-weight a significant tumor response as not dose-related. If this is true, then all the tumor responses observed in all groups are incidental. Thus, it would be reasonable, if the conclusion is that the tumor response is not dose-related, to compare the responses in all the animals in a study to historical controls, not just those assigned randomly to the study control group. The EPA (2005) *Cancer Guidelines* properly recommend caution in the use of historical control data: "Generally speaking, statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average. Random assignment of animals to groups and proper statistical procedures provide assurance that statistically significant results are unlikely to be due to chance alone." Moreover, a careful review of historical control data to ensure comparability directed by the *Guidelines* was not described. Thus, some Panelists found that reliance on historical control data in the EPA (2016a) weight-of-evidence evaluation was overdone, and not done in accordance with EPA (2005) *Guidelines*.

Pairwise Tests

In several cases EPA (2016a) used the non-significance of pairwise tests to down-weight a significant trend test. This is contrary to EPA (2005) *Cancer Guidelines* which state: "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result." As noted above, the EPA (2016a) analysis would be on a sounder and more easily interpreted footing if it eschewed a battery of pairwise tests, and instead conducted a single powerful test for carcinogenicity, namely a trend test.

Disregard of exposures > 1000 mg/kg/day

The EPA (2016a) practice of disregarding or giving low weight to results at exposures > 1000 mg/kg/day, seems to be at odds with the EPA (2005) *Cancer Guidelines*, which suggest that an excessively high dose would be "5% of the test substance in the feed for dietary studies." But 5% in feed is considerably greater than 1000 mg/kg/day in both rats and mice, and none of the doses utilized in the studies reviewed exceeded 5% in feed. Several Panel members saw no overriding reason for disregarding results from exposures > 1000 mg/kg/day, so long as the dose does not exceed the maximum tolerated dose. These Panelists also thought that responses at such

doses may have relevance for human risk, as the presence of a response at a high dose suggests that there possibly could be risks at lower doses that were too low to be detected because of reduced power at lower doses. One Panelist commented that the definition of limit dose was for the design of animal bioassay studies, and should not be applied to the interpretation of the results of studies designed under the *Guidelines*.

Weight-of-evidence assessment in the presence of a large number of bioassays

All of the shortcomings discussed in the previous paragraphs are in the direction of making a conclusion of no carcinogenic effect. However, in the opinion of some Panel members, it seems likely that these shortcomings are more than compensated for by focusing on the statistical significance of the tumor types showing most extreme dose-responses among a very large number of tumor types for which data are available. With such a large number of tumor types available for statistical evaluation in an animal study (e.g., 100+), several tumor types would be expected to be significant at the $P = 0.05$ level, even if the treatment has no effect on tumor occurrence. Other Panelists recommended two other perspectives for determining weight-of-evidence in the presence of a large number of bioassays: one perspective is based on interpretation of the current wording of the *Guidelines*, and the other recommends the Agency implement pooled analyses. See the discussion in response to charge question 3b for further details describing three different approaches to handling multiple bioassays and the justification for these various approaches.

Concluding comments

The EPA Issue Paper concluded that the observed tumor responses correspond to common spontaneous tumor types, which are unrelated to glyphosate treatment. Some Panel members agreed. Other Panel members interpreted the totality of the tumor data as supporting the hypothesis that glyphosate causes the promotion or progression of common spontaneous lesions and considered the observed degree of bioassay irreproducibility is expected given differences in rodent genetics, study design and study quality. Some Panel members agreed that there is sufficient evidence to conclude glyphosate is a weak rodent carcinogen.

4. As part of its analysis, the agency has considered almost 200 assays investigating the genotoxic potential of glyphosate. Of these, 107 were performed with the active ingredient glyphosate. These included *in vitro* and *in vivo* studies from the open literature, as well as studies submitted to the agency that were conducted according to Office of Chemical Safety and Pollution Prevention (OCSPP)/ Organization for Economic Cooperation and Development (OECD) guidelines. Non-mammalian studies were excluded from this analysis unless the assays were generally recognized to inform the human carcinogenic potential of glyphosate (e.g., bacterial reverse mutation assays). Studies evaluated genotoxic endpoints, such as gene mutations in bacteria and mammalian cells, chromosomal aberrations, micronuclei formation, and other assays measuring DNA damage.

a. Please comment on the agency's review and evaluation process of relevant genotoxicity studies to inform the human carcinogenic potential of glyphosate, including the decision to exclude non-mammalian studies (e.g., reptiles, plants, worms, fish), except those generally recognized to inform human carcinogenic potential.

Panel Response

Panel members agreed that the review and evaluation process of genotoxicity studies is sufficient given the limits of the accepted assays, which are described in the report (first paragraph of section 5.1) as being sufficient to detect: "1) changes in single base pairs, partial, single or multiple genes, or chromosomes, 2) breaks in chromosomes that result in transmissible deletion, duplication or rearrangement of chromosome segments, and 3) mitotic recombination."

One Panel member recommended that this section of the document be expanded to indicate that none of the assays employed provides an unbiased (global) measure of small insertions, deletions and rearrangements, which can result in gene copy number variation (CNV). CNVs are best resolved using sequence-based approaches and are important for several reasons. CNVs are now known to occur at greater rates than other types of mutations and can arise both meiotically and somatically. CNVs arise via mechanisms that differ from base-substitution mutations, including inhibition of replication, which some studies have reported for glyphosate (Marc et al., 2002 and 2004). Structural mutations may contribute to human variation at least as much or more than base-substitution mutations. Further, strong associations have been observed between CNVs and many cancers, cancer risk factors, and mechanisms for promotion. Finally, there seems to be some evidence that structural mutations contribute to response to glyphosate exposure (Gaines et al., 2010; Widholm et al., 2001).

One Panel member encouraged the agency to consider two key human biomonitoring studies in their evaluation of genotoxicity, specifically studies by Bolognesi et al. (2009) and Koureas et al. (2014). Bolognesi et al. (2009) evaluated genotoxicity as binucleated micronuclei and observed some increases in the blood cells of Columbian farmers after aerial spraying of glyphosate. Koureas et al. (2014) measured oxidative DNA damage as 8-hydroxy-2' - deoxyguanosine (8-OH-dG) and reported that glyphosate applicators more often had high levels of 8-OH-dG than non-applicators (43.8% vs 27.9%, RR=1.47, 95% CI=0.78, 2.77).

Because some Panel members concluded that the rodent bioassay data indicates that at high dose, dietary exposure to glyphosate causes promotion/progression of pre-existing spontaneous lesions, studies in mammalian and non-mammalian species are of interest in terms of understanding potential underlying mechanisms of promotion/progression. Disruption of the proteome is one potential non-genotoxic mechanism of carcinogenesis. A recent study by Ford et al. (2017), concluded that *in vivo* glyphosate exposure may lead to generation of reactive metabolites such as glyoxylate which may in turn inhibit fatty acid oxidation enzymes, heighten levels of triglycerides and cholesteryl esters, and may potentially lead to metabolic disorders stemming from impaired fatty acid oxidation or fatty acid metabolism, including obesity, hepatic steatosis, atherosclerosis, and dyslipidemia.

Panel members agreed that, in the determination of whether or not glyphosate is likely to be genotoxic in humans, the EPA document focuses appropriately on studies conducted in cultured mammalian cells and exposed animal models.

b. Consistent with the OECD guidance (2015), *in vivo* findings in genetic toxicology testing are generally considered as having a greater relevance to humans than *in vitro* findings.

Consistent with the 2005 *Cancer Guidelines*, all available data were considered in the weight-of-evidence evaluation of the genotoxic potential for glyphosate. The relevant studies are summarized in Tables 5.1-5.7. Please comment on the agency's approach for evaluating the genotoxicity data.

Panel Response

The Panel found that the agency has assembled and evaluated relevant genotoxicity data in an appropriate manner, with the previously mentioned caveat regarding the lack of robust detection of CNVs.

c. As described in Section 1.4, oral exposure is considered the primary route of concern for glyphosate and high-end estimates of exposure range from 0.47-7 mg/kg/day. Please comment on the human health relevance of the genotoxicity findings with respect to the doses where effects were observed and the route of administration.

Panel Response

Panel members agreed that genotoxicity studies were conducted at sufficiently high doses (and range of doses). There is a sufficient number of negative studies, where glyphosate was administered through the oral route, to support the agency's conclusion that glyphosate is not genotoxic. A few positive findings in studies employing high dose exposures through the intraperitoneal (IP) route of administration may represent secondary effects of toxicity.

Several Panel members commented that if glyphosate causes progression of spontaneously arising lesions (cells carrying cancer driver mutations or other types of DNA damage), then humans are at risk of glyphosate-induced carcinogenicity and the longer human lifespan (as compared to rodents) is expected to contribute to the risk.

d. Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available genotoxicity studies, as described in Section 5.7.

Panel Response

Panel members found that the Agency's overall weight-of-evidence and conclusion that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route are sound. Areas of remaining uncertainty are related to the potential for glyphosate-induced inflammation and genotoxic effects secondary to toxicity caused by high dose exposures (i.e., glyphosate-induced inflammation, oxidative stress, 8-OH-dG, and sister chromatid exchanges or SCE) and whether the glyphosate-containing formulations have genotoxic potential.

5. The modified Bradford Hill criteria were used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance, and biological plausibility. In accordance with the 2005 *Cancer Guidelines*, the agency used a weight-of-evidence analysis to characterize the human carcinogenic potential of glyphosate and determine which cancer descriptor is supported by the data. The agency has described

the strengths and uncertainties associated with the choice of various cancer descriptors with a focus on "suggestive evidence of carcinogenic potential" and "not likely to be carcinogenic to humans". Please comment on the completeness, transparency, and scientific quality of the agency's characterization of the carcinogenic potential.

Panel Response

The Panel was asked to comment on the completeness, transparency and scientific quality of the argument presented in the EPA's Issue Paper leading to the conclusion (page 141) that "The strongest support is for 'not likely to be carcinogenic to humans' at doses relevant to human health risk assessment." The Issue Paper's goal is to describe the Agency's "comprehensive analysis of available data from submitted guideline studies and the open literature." (page 140)

The Panel noted that the conclusion on glyphosate carcinogenicity offered in the Issue Paper has two parts. The first part is a hazard statement; the second part is a risk characterization statement. Since the Issue Paper is not a full risk assessment of technical glyphosate as outlined in the 2005 *Guidelines for Carcinogen Risk Assessment*, the Issue Paper conclusion is best assessed as a hazard statement.

This Issue Paper is conceptually driven by the 2005 *Guidelines for Carcinogen Risk Assessment* which in turn incorporates the "modified Bradford Hill Criteria to evaluate strength, consistency, dose response, temporal concordance and biological plausibility of multiple lines of evidence in a weight-of-evidence analysis" (page 14). The Issue Paper also draws on the 2010 EPA OPP draft "*Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment*" which also utilizes a modified Bradford Hill Criteria as applied specifically to epidemiologic data.

Completeness of Agency's carcinogenic potential characterization

For the epidemiology studies, the Agency followed its peer-reviewed guidelines on evaluation and use of epidemiology studies in risk assessment and reviewed:

- Study design, including study sample size and power to detect effects under consideration,
- The quality of the exposure assessment in epidemiology studies,
- The potential for differential and non-differential misclassification of effects or outcomes,
- The measurement and utilization (or not) of potential confounders,
- Potential biases and their impacts on observed associations, and
- The associated statistical analysis.

For the animal studies, the Issue Paper review followed standard practice and considered in their review, in order to ultimately select and interpret the findings from well-conducted, long-term animal studies:

- Study design, sample size, and adherence to quality guidelines,
- Statistical analysis and use of trend and multiple comparison testing protocols,
- Concurrence with historical control rates,
- Evidence of carcinogenicity through magnitude of tumor response, occurrence at multiple sites, in multiple strains or species, their progression, latency, and dose response, and,
- Absence of tumors.

For genotoxicity studies, the Issue Paper review also followed standard practice and considered:

- Test type and objective,
- Substance tested (e.g. technical glyphosate),
- Quality of the implementation of the study (adherence to standard study design, sample size, dose, use of positive and negative controls),
- Conditions under which the study was performed (solubility, pH, osmolarity, cytotoxicity, but also degree of blinding in evaluation of outcomes), and,
- Consistency among findings and support for particular MOA.

By any criteria, this list suggests a complete review. However, as the Panel notes in earlier sections of this report, there are aspects of EPA's approach and conclusions that it recommends altering. Missing are:

- Study data and results on workers engaged in manufacturing, formulating and handling and wholesale selling of glyphosate – although mentioned a number of times in the Panel's discussions, it is generally assumed that there are no worker epidemiology studies because none are reported in the Issue Paper.

- Other human incident data, such as reports on acute accidental exposures – the 2010 EPA OPP draft "*Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment*" discusses the utility of other incident data. While incident data have little direct relevance to cancer outcomes, time trends suggesting increasing episodes of acute exposures can also be suggestive of increases in overall exposure over time, which can in turn affect inferences about the quality and biases in the human epidemiologic studies.

Transparency (interpreted by the Panel as honesty and openness) of Agency's carcinogenic potential characterization

The Panel did not have major issues in following the Agency's assessment. Section 6.6 of the Issue Paper is clear in laying out the Agency's argument for its final classification. Supplemental documents provided on the meeting docket allowed Panel members the information necessary to duplicate most analyses and verify most report claims if so desired. While this document indicates areas where Panel members disagree with the Agency's assessment (see next section), the Panel was able to identify documents and data from which Issue Paper claims originated. The Panel expressed concern that a barrier to full transparency exists in that some of the documents and associated data that are used by EPA in this assessment require special procedures for access and a few studies were not available to the Panel or the public. The Agency explained that FIFRA regulations are responsible for some of these limitations. Regardless, the Panel wondered whether the public could fully review and reproduce the conclusions reached by EPA.

Scientific quality of the Agency's carcinogenic potential characterization

Quality science is reproducible, free from distortion, credible, built on what is known (sound science), follows logical inferences, and is honest about what is achievable and the limits of available designs and data. While the Issue Paper does try to detail the design and data limitations of each study selected, some on the Panel believed that it does not provide sufficient details to support its conclusions (for example, see discussion of Charge Question 3e) and this negatively impacts the scientific quality of the report. In addition, many Panel members felt that some of the discussions of study design and data limitations provided in the Issue Paper introduced and used criteria that were not part of EPA *Guidelines* for these assessments, and this further reduces the credibility of the assessment.

The issue of distortion impacts the nature and quality of the inferences drawn in the Issue Paper. These inferences also depend upon a consistent application of the Bradford Hill Criteria, aspects of which are discussed in the next sections.

Dose-response and temporal concordance

With regard to the epidemiology data, the Issue Paper concludes: "Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data" [page 68]. The 2005 *Guidelines* state (page A-2): "When cancer effects are not found in an exposed human population, this information by itself is not generally sufficient to conclude that the agent poses no carcinogenic hazard to this or other populations of potentially exposed humans, including susceptible subpopulations or life stages."

The Panel debated the Issue Paper's assignment of weights and arguments that lead to its conclusion of "no observed association". The issues considered by the Panel and on which there was disagreement are as follows.

1. Some Panel members noted that weight placed on the findings from the prospective Agricultural Health (cohort) Study (AHS, 2005) is too high given that this study has had only

limited follow-up to date, is subject to selection bias due to its approach to recruitment (i.e. preferentially excluding cases that occur before the enrollment in the cohort) and uses biased exposure quantification in the analysis. An updated report is expected to clarify some of these issues, and is expected within the year.

2. The Panel could not agree on the appropriate weights to be applied to the Eriksson et al. (2008) and McDuffie et al. (2001) studies. Some Panel Members felt that that these studies provide positive evidence of a dose response to glyphosate exposure and hence should be afforded greater weight. Other Panel Members noted that the potential impacts of recall and selection biases on study findings are not properly accounted for in the Issue Paper's assessment and as a result these studies are afforded too much weight.

3. Some Panel members noted that the Issue Paper's discussion of the change-in-use patterns and their impact on risk estimates expected from the epidemiology (pages 129-130) does not reflect a good understanding of the estimates being reported. The Issue Paper's analysis appears to be aligning assumptions about absolute production changes over time with epidemiological inferences for relative impacts of exposure in ways that many on the Panel felt cannot be supported. It makes assumptions about the change of patterns of exposure based on trends in sales (production trends), that do not necessarily reflect the more relevant (but unknown) pounds per worker per year (relevant exposure metric). Trends in production can only be speculated to affect usage at the worker level. In documents presented to the Panel, the Center for Food Safety provided a compilation from USDA data (EPA-HQ-OPP-2016-0385-0438) showing evidence, based on pounds per acre per year, that glyphosate use in the 1980's may have resulted in potentially higher per worker exposure than in the 1990's, including after the large increase in glyphosate production. This argument is in direct contradiction to the arguments made in the Issue Paper. The Issue Paper's arguments about exposure trends also ignore latency. Since all the arguments in the paragraph beginning at the bottom of p. 129 (and also made in Section 3.6) rely on speculation and unverified assumptions, the Panel recommends they be removed from the Issue Paper.

4. Some Panel members interpreted the meta-analysis results for NHL to be indicative of a suggestive effect of glyphosate. Other Panel members felt that the limitations of the retrospective case-control studies, particularly with respect to recall bias, selection bias, and confounding by other aspects of living or working on a farm, combined to render the meta-statistics unreliable.

For the rodent carcinogenicity assay data, the Issue Paper concludes (page 96), "based on the weight-of-evidence, the agency has determined that any tumor findings observed in the rat and mouse carcinogenicity studies for glyphosate are not considered treatment-related. Tumor findings observed at the highest doses tested were also not reproduced in studies in the same animal strain at similar or higher doses." The 2005 *Guidelines* state (page A-4): "When cancer effects are not found in well-conducted animal cancer studies in two or more appropriate species and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess human carcinogenic potential, in the absence of human data to the contrary." The 2005 *Guidelines* also state (page A-3): "The default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans."

The Panel debated at length the Issue Paper's interpretation of positive tumor responses in rodent bioassays. Not all Panel members agreed with the Issue Paper's conclusion that findings in rodent bioassays are not treatment-related. The discussion centered on which analysis results constitute a significant finding and which support a false positive finding. Not everyone agreed with how the Issue Paper assigned weights/influence to non-monotonic dose-responses, to significant pairwise comparisons, and to comparisons with historical control data. Some Panelists felt that the Issue Paper did not take into consideration the number of statistical tests performed when assessing tumor incidence across rodent bioassays. Also discussed was the inference possible from using pooled analyses to draw gender- and species-specific conclusions from the multiple studies on each endpoint, and the impact of using exact *P-values* versus approximate or asymptotic *P-values* in the standard test used to evaluate evidence for dose response. Finally, there was discussion on the appropriateness and desirability of down-weighting results at doses that exceeded 1000 mg/kg-BW/day.

Following these discussions, some Panel members interpreted the positive animal bioassay findings as likely false positives, resulting from the very large number of statistical tests conducted, and concluded that there is no credible evidence of a dose response, thus agreeing with the conclusions of the Issue Paper. Other Panel members interpreted the significant trend test results as well as other rodent bioassay findings as sufficient evidence to conclude that glyphosate is a rodent carcinogen. Under the 2005 *Guidelines* these findings are adequate to support a conclusion that glyphosate can have carcinogenic potential in humans (more details are provided in the section on *Evaluation and Proposed Conclusion* discussion below).

For the genotoxicity studies, the Issue Paper concludes (page 128): "The overall weight-of-evidence indicates that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route" and "While there is limited evidence (of) genotoxic(ity) for effects in some *in vitro* experiments, *in vivo* effects were given more weight than *in vitro* effects particularly when the same genetic endpoint was measured, which is consistent with current OECD guidance. The only positive findings reported *in vivo* were seen at relatively high doses that are not relevant for human health risk assessment."

The Panel generally agreed with the Issue Paper's conclusion regarding the lack of genotoxicity effects of glyphosate.

Strength, consistency and specificity

With regard to the epidemiology studies, the Panel concurred with the Issue Paper conclusions regarding solid tumors, leukemia, MM and HL. Panel members differed in their agreement with the Issue Paper's conclusions regarding the strength, consistency and specificity of the epidemiological findings for a relationship between glyphosate exposure and NHL.

Some Panel members remarked on the consistency in the direction and value of the estimated odds ratios across multiple high-quality studies, illustrated by the very low heterogeneity statistic in the meta-analyses. They argued that the best quantification of the NHL evidence is provided by the meta-analyses with risk estimates of around 1.3 to 1.5 and with a lower bound around 1.0 but typically slightly above one when estimates are reported to 2 significant digits. Some Panel members found that the Issue Paper conclusion that the

epidemiology studies report conflicting results for NHL is based on a *post hoc* sorting of studies (see p. 130) that is not based on statistical evidence. The apparent inconsistency of the dose-response estimates is thus a result of this invalid and unsupported comparison, and this analysis finding should not be given any weight in the assessment. Some Panel members believed that the Issue Paper should rely on the meta-analysis results as the best estimate of the NHL effect, while other Panel members noted that meta-analyses cannot compensate for or remove residual confounding in the original studies. In other words, they stressed that if the individual studies present biased estimates, then the meta-result will also be biased.

The Panel discussion on the strength of findings in the animal carcinogenicity studies centered on the value of findings for doses that exceeded 1000 mg/kg-BW/day (the limit dose). The limit dose is used in the *Cancer Guidelines* as a design criterion (EPA 2005). Several Panelists noted that once an experiment is designed, interpretation of its findings should take into account all the data that were obtained under that design. The Panel consensus was that the Issue Paper needs to refine and strengthen its argument regarding this issue; it needs to clarify the use of the *Cancer Guidelines*, discuss in detail studies that might argue for or against the use of limit dose findings in tests, and ensure the 2005 *Cancer Guidelines* are adhered to in their revised approach. For many on the Panel, this criterion is viewed as having high potential to distort findings, and as such needs more careful discussion in the Issue Paper.

The Panel discussed at length the consistency, or lack thereof, of animal findings. In particular, some Panelists noted that although some individual rodent bioassays reported statistically significant results with regard to one or more tumor-types, these specific results were not replicated in other studies using the same rodent species and strain, even when replicate bioassays were run at higher doses. In evaluating the toxicology evidence from the rodent bioassays, pooling of animal data for dose-response modeling provides the equivalent of the meta-analysis performed for the epidemiology data. Dose response modeling results from pooled analysis, along with proper consideration of multiple comparisons, would provide a better base from which to discuss qualitatively the consistency of study findings for specific endpoints, species and in many cases, sexes.

One Panel member presented an argument that there is sufficient replication and magnitude of bioassay results to demonstrate treatment-related increases in rat hepatocellular adenoma, mouse lung adenoma/adenocarcinoma, and mouse lymphoma. The Panelist pointed to glyphosate-induced lymphoma in mice, where two of four studies (employing 50 mice/group) reported increases in lymphocytic hyperplasia in treated mice and three reported increases in lymphoma (including malignant lymphoma). Other Panel members agreed with this argument, particularly when examined with findings from a pooled analysis offered by a public commenter, Dr. Christopher Portier (EPA-HQ-OPP-2016-0385-0449).

Biological plausibility and coherence

Some Panel members recommended that the plausibility argument in the Issue Paper should be updated to address the hypothesis that glyphosate has potential to be a weak cancer promoter. Some on the Panel remarked that the hypothesis that glyphosate could be a weak promoter is not addressed in the Issue Paper. They feel that glyphosate as a weak promoter is a

potential explanation for the human and rodent study NHL and lymphoma results. These concerns also suggest the need for more discussion on immunotoxicity by glyphosate.

One Panelist commented that the epidemiology studies provide plausible evidence of a link between NHL occurrence and glyphosate exposure, a link that does not depend upon or require that the mechanisms driving this association are fully understood. This situation was compared to the evidence for air pollution health effects that are primarily based on findings from epidemiology studies, noting that it is only in recent years that mechanistic explanations have begun to emerge from toxicology and other experimental study findings to support these associations. In air pollution setting, relative risk estimates for an increment in pollution exposure are on the order of 1.03 for short-term acute effects estimated by time series studies, to 1.25 for longer-term chronic effects estimated in cohort studies. A similar evolution of understanding is plausible for glyphosate exposure.

Uncertainty

The Panel found that this section appropriately notes that the available database is remarkably large and should be adequate for evaluating carcinogenic potential but that many uncertainties remain. Some uncertainties brought forward from earlier sections in the Issue Paper, such as excluding formulations with glyphosate and weak pharmacokinetics could be expanded upon in this section. Uncertainties in epidemiological and animal study evidence are well discussed in earlier sections.

Some Panel members focused on the non-significance (i.e., *P-values* greater than 0.05) of odds ratios for the NHL analyses in the individual epidemiology studies, and that estimates of the lower bound of the 95 percent confidence interval of the odds ratio was at or below one across all studies. Various meta-risk estimates ranged between 1.3 and 1.5 and all had confidence interval lower bounds at or above 1.0. Given the potential for biases in estimates resulting from problems with exposure estimation, recall, and participant selection, as were pointed out in the Issue Paper, this relatively small but elevated risk with confidence interval lower bounds close to 1.0 did not argue for a strong and consistent finding of effect. In particular, in the opinion of some Panel members, the Issue Paper does not adequately assess the impact of potential biases on the odds ratio estimates, recall and selection bias in particular.

Evaluation and Proposed Conclusion

The Issue Paper concludes in Section 6.6.2 that the weight-of-evidence supports the descriptor for glyphosate of "not likely to be carcinogenic to humans" at the doses relevant to human health. The argument for concluding this classification rests on the assessment conclusion that there is "convincing evidence that carcinogenic effects are not likely below a defined dose range" where the data are "robust for deciding that there is no basis for human hazard concern."

The Panel discussion mainly focused on how the Issue Paper did or did not argue for a hazard determination of "not likely to be carcinogenic to humans." Most of the Panel's discussion centered on assessment of the potential for glyphosate to be a carcinogen, and less on the conditions under which glyphosate exposure would represent a significant human health risk. In the Issue Paper, the statement "at doses relevant to human health" establishes a condition

under which glyphosate is "not likely to be carcinogenic to humans." The Panel discussions on the strength of association between glyphosate exposure and cancer incidence in the epidemiological studies, and the discussions on dose response in animal studies focused on assessing carcinogenic potential (at any dose) and less on establishing a threshold for risk to human health. This focus on the hazard identification is appropriate for an evaluation of the carcinogenic potential, as framed by EPA's 2005 *Guidelines* that describes hazard assessment as the first step of a risk assessment. For hazard evaluation, the question to be addressed is "Can the identified agent present a carcinogenic hazard to humans and, if so, under what circumstances?" (pp. 1-3)

The Panel was split between those members agreeing with the Issue Paper conclusions and those members who felt that the characterization of "not likely to be carcinogenic to humans" in the Issue Paper should be replaced by the hazard descriptor of "suggestive evidence of carcinogenic potential".

Perspectives supporting the "not likely to be carcinogenic to humans" descriptor

Some Panel Members concluded that while many of the issues identified in the Panel discussions can and should be addressed in the final EPA report on glyphosate, these changes would unlikely, in the opinion of these Panel members, change the final Issue Paper conclusions. They referenced a) a presentation before the panel by Dr. Haseman showing that the number of statistically significant responses in the glyphosate rodent bioassays is no greater than would be expected by chance, and b) a corroborating analysis presented by one Panel member. These arguments support their conclusion that the bioassay results are consistent with what would be expected by chance and not reflective of compound-induced effects. They see a wealth of studies with insufficiently consistent findings; several entirely negative bioassays, several weakly positive bioassay findings but not in the same tumor type, and, not in a majority of studies. These Panel members also concluded that the weakly positive results on NHL from the human case-control studies cannot be definitively linked to glyphosate-exposure, and biases from residual confounding due to other, non-glyphosate aspects of farming, recall bias, or selection bias are more likely explanations of these findings. The reproducible negative genotoxicity findings do not suggest a mutagenic MOA for glyphosate, and the Issue Paper presents no evidence that glyphosate is immunotoxic. Taken altogether, these findings are not sufficient to raise the hazard above "not likely to be carcinogenic to humans."

Some panel members did not agree with the premise that the rodent bioassay data indicate significant carcinogenic effects at doses that do not greatly exceed EPA's high-end estimate of occupational glyphosate exposure of 7 mg/kg-bw/day. In the opinion of these panel members, the rodent study results are more likely simply examples of the many incidental findings that are to be expected in a large database like the glyphosate animal database. Specifically:

1. In addition to the increases in the occurrence of lymphocytic hyperplasia cited in Lankas (1981) and referenced above there was a significant deficit of lymphatic hyperplasia among dosed animals at one site. More importantly, among Lankas (1981) and four other studies in Sprague-Dawley rats employing doses of between 30 and 40 times the highest dose used in Lankas (1981), none showed any evidence of an effect of glyphosate exposure upon lymphoid tumors.

2. In the lymphoid hyperplasia in Wood 2009b referenced above, lymphoid hyperplasia was detected in 4/36 male control mice, 1/1 low dose, 1/1 mid dose, and in 3/32 high dose male mice. Thus the claims of lymphoid hyperplasia at low and mid doses are both based on only one exposed animal each.

3. As noted in point 1, there are four bioassays in the same strain of rat employing doses of between 30 and 40 times the highest dose used in Lankas (1981). None of these bioassays show any evidence of an effect of glyphosate exposure upon testicular tumors (All of the responses in these bioassays are shown in Table 2).

4. The trend test was not significant in the response of pancreatic islet cell adenoma among male Sprague-Dawley rats in Stout and Ruecker 1990. However, significant negative trends occurred in female rats for both adenoma and adenoma and carcinoma combined. Two other studies in Sprague-Dawley rats and three in Wister rats all tested at a higher dose than Stout and Reucker, but found no evidence of a positive effect of glyphosate exposure upon these tumors. However, Atkinson 1983 found a highly significant negative trend in adenoma among male Sprague-Dawley rats.

Perspectives supporting the "suggestive evidence of carcinogenic potential" descriptor

Other Panel members did not agree with the conclusions of the Issue Paper. To these Panel members, the weight-of-evidence conclusion based on EPA's 2005 *Guidelines* naturally leads to suggestive evidence of potential carcinogenic effects. In their view, epidemiologic and rodent studies contain findings that together (coherence and consistency) suggest a potential for glyphosate to affect cancer incidence. Many of the arguments put forth in the Issue Paper discussion are not persuasive. These Panelists concluded that the epidemiologic and rodent study findings should not be discounted to the extent done in the Issue Paper. One Panel member argued that, using standard approaches in the analysis of the glyphosate rodent bioassay data, significant carcinogenic effects are observed at doses that do not greatly exceed EPA's high-end estimate of occupational exposure of 7 mg/kg-bw/day. Specifically noted are:

1. Lymphocytic hyperplasia at 11 mg/kg-bw/day in Sprague-Dawley rats in Lankas, 1981.

2. Lymphoid hyperplasia at low and mid doses in males at 71.4 and 234.2 mg/kg-bw/day in a study where malignant lymphomas were significantly induced at 810 mg/kg-bw/day in Wood et al. 2009b.

3. Testicular interstitial tumors in male Sprague-Dawley rats demonstrated a significant trend and a significant pairwise comparison between control and the high dose of 31.49 mg/kg-bw/day in Lankas, 1981.

4. Pancreatic islet cell adenoma in male Sprague-Dawley rats demonstrating a significant pairwise comparison relative to controls at the low dose, 89 mg/kg-bw/day in Stout and Ruecker, 1990.

According to the 2005 EPA *Guidelines for Carcinogen Risk Assessment*, the cancer descriptor "not likely to be carcinogenic to humans" applies if "there is convincing evidence that carcinogenic effects are not likely below a defined dose range." Many Panel members believe

that the EPA did not provide convincing evidence of a lack of carcinogenic effects. These Panelists agreed that the four findings listed above are adequate to reject the Issue Paper's conclusion of "not likely to be carcinogenic to humans" and support a conclusion of "suggestive evidence of carcinogenic potential" under these *Guidelines*.

Other perspectives

Some Panel members disagreed with the conclusion that the descriptor should be "suggestive evidence of carcinogenic potential" and some of these Panelists also did not feel comfortable with the descriptor "not likely to be carcinogenic to humans" either, preferring a descriptor such as "no credible evidence of carcinogenicity" or "equivocal."

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APPENDIX 1 – WRITTEN SUBMISSIONS TO DOCKET NO. EPA-HQ-OPP-2016-0385

Commenter*
Anonymous public comments
Comment submitted by Dag Falck, Organic Program Manager, Nature's Path Foods Inc.
Comment submitted by A. DeLuca
Comment submitted by A. Lewis
Comment submitted by A. Schneiderman
Comment submitted by A. Sorrells-Washington
Comment submitted by Aaron Hobbs, President, RISE, Responsible Industry for a Sound Environment
Comment submitted by Amechi Chukwudebe, PhD, BASF
Comment submitted by Amelia Jackson-Gheissari PhD, International Regulatory Affairs Manager and Donna Farmer, PhD, Senior Toxicologist, Monsanto Company
Comment submitted by Amy (no surname provided)
Comment submitted by Andrew Behar, Chief Executive Officer, As You Sow, et al.
Comment submitted by Anthony Samsel, Research Scientist, Consultant, Samsel Environmental and Public Health Services (SEAPHS)
Comment submitted by B. Talen
Comment submitted by B. Tarone
Comment submitted by Bill Freese, Science Policy Analyst, Center for Food Safety (CFS)
Comment submitted by C. A. Harris, PhD, FRSC et al.
Comment submitted by C. J. Portier, PhD
Comment submitted by C. Laieski
Comment submitted by Center for Regulatory Effectiveness (CRE)
Comment submitted by Christine T. (no surname provided)
Comment submitted by Christopher P. Wild, PhD, Director, International Agency for Research on Cancer (IARC)
Comment submitted by D. Brusick et al.
Comment submitted by D. Davis
Comment submitted by D. Norris
Comment submitted by D. Pompeo
Comment submitted by D. Schubert
Comment submitted by D. Sutherland
Comment submitted by Dale Moore, Executive Director, Public Policy, American Farm Bureau Federation (AFBF)
Comment submitted by Daniele Court Marques, Pesticides Unit, European Food Safety Authority (EFSA)
Comment submitted by Danielle (no surname provided)
Comment submitted by David Spak, Stewardship Manager, Bayer Vegetation Management
Comment submitted by Deborah Larson Hommer, President, Virginians for Medical Freedom (VMF)
Comment submitted by Dennis D. Weisenburger, MD, Professor, Chair, Department of Pathology, City of Hope

Commenter*
Comment submitted by Dev Gowda, J.D., Toxics Advocate, U.S. Public Interest Research Group (PIRG)
Comment submitted by Donna Farmer, PhD. Senior Toxicologist, Monsanto Company
Comment submitted by Dow AgroSciences
Comment submitted by E. Crouch
Comment submitted by E. Springwind
Comment submitted by E. Stockman
Comment submitted by E. Wilson
Comment submitted by Emily Marquez, Ph.D., Staff Scientist, Pesticide Action Network North America (PANNA)
Comment submitted by G. Stromberg
Comment submitted by Gordon Stoner, President, National Association of Wheat Growers (NAWG)
Comment submitted by Gretchen DuBeau, Esq., Executive and Legal Director, Alliance for Natural Health USA
Comment submitted by H. Rowland
Comment submitted by I. Panton
Comment submitted by Intertek Scientific & Regulatory Consultancy
Comment submitted by J. Hoy
Comment submitted by J. Littrell
Comment submitted by J. Manning
Comment submitted by J. Moore
Comment submitted by J. Young
Comment submitted by James S. Bus PhD, DABT, ATS, Exponent, Inc. on behalf of CropLife America
Comment submitted by Janet E. Collins, Ph.D., R.D., Senior Vice President, Science and Regulatory Affairs, CropLife America (CLA)
Comment submitted by Jennifer Sass, PhD, Senior Scientist, Natural Resources Defense Council (NRDC)
Comment submitted by John Weinand, President, North Dakota Grain Growers Association (NDGGA)
Comment submitted by Joseph K. Haseman, J. K. Haseman Consulting
Comment submitted by K. Lundsford
Comment submitted by K. Taylor
Comment submitted by Kevin Bradley, President, Weed Science Society of America (WSSA)
Comment submitted by L. Garvey
Comment submitted by L. Staman
Comment submitted by Lars Niemann, Toxicology of Active Substances and their Metabolites Unit, Department Safety of Pesticides, German Federal Institute for Risk Assessment (BfR), Berlin
Comment submitted by Luther Markwart, Executive Vice President, American Sugarbeet Growers Association and Co-Chairman, Sugar Industry Biotechnology Council
Comment submitted by M. Bosland

Commenter*
Comment submitted by M. McLean
Comment submitted by M. Moore
Comment submitted by M. Pybus
Comment submitted by M. Wilkus
Comment submitted by Montague Dixon, Senior Regulatory Manager, Syngenta Crop Protection, LLC
Comment submitted by Ms. Delgado
Comment submitted by N. Paffrath
Comment submitted by Nathan Donley, Ph.D., Senior Scientist, Environmental Health Program, Center for Biological Diversity
Comment submitted by Nichelle Harriott, Science and Regulatory Director, Beyond Pesticides
Comment submitted by Nufarm Americas Inc
Comment submitted by P. A. Fenner-Crisp
Comment submitted by P. Whitman
Comment submitted by Pamela Koch, EdD, RD, Executive Director Laurie M. Tisch Center for Food, Education & Policy, Teachers College, Columbia University
Comment submitted by Peter F. Infante, Consultant, Peter F. Infante Consulting, L.L.C.
Comment submitted by Philip W. Miller, Ph.D., Vice President, Global Regulatory and Government Affairs, Monsanto Company
Comment submitted by R. Andrews
Comment submitted by R. Briggs
Comment submitted by R. E. Tarone
Comment submitted by R. Mason
Comment submitted by R. Parsons
Comment submitted by R. Tarone
Comment submitted by Rebecca St James (no surname provided)
Comment submitted by Reece Langley, Vice President, Washington Operations, National Cotton Council (NCC)
Comment submitted by Richard D. Gupton, Senior Vice President, Public Policy & Counsel, Agricultural Retailers Association (ARA)
Comment submitted by Richard Wilkins, President, American Soybean Association (ASA)
Comment submitted by Robert P. DeMott, Principal Toxicologist, Ramboll Environ on behalf of The Scotts Company LLC
Comment submitted by S. Seneff
Comment submitted by S. Barr
Comment submitted by S. Gardon
Comment submitted by S. Stair
Comment submitted by S. Vose
Comment submitted by S. Young
Comment submitted by Scott Slaughter, The Center for Regulatory Effectiveness (CRE)
Comment submitted by Steve Levine, Ph.D., CropLife America (CLA)
Comment submitted by T. Tokuda

Commenter*
Comment submitted by Tony Tweedale, R.I.S.K. (Rebutting Industry Science with Knowledge) Consultancy
Comment submitted by W. Beck
Comment submitted by W. Fawell
Comment submitted by Wenonah Hauter, Executive Director, Food & Water Watch
Comment submitted by Zen Honeycutt, Executive Director, Moms Across America
Mass Comment Campaign submitted by Alexis Baden-Mayer, Organic Consumers Association
Mass Comment Campaign submitted by Jennifer Listello, Existing Chemistry Global Coordinator, Monsanto
Mass Comment Campaign submitted by Tiffany Finck-Haynes, Friends of the Earth
Mass Comment Campaign submitted by Alliance for Natural Health USA
Mass Comment Campaign submitted by Food and Water Watch
Mass Comment Campaign submitted by Tiffany Finck-Haynes, Friends of the Earth

*Note: some commenters provided multiple submissions to the docket.

EXHIBIT 15

Summary of ORD comments on OPP's glyphosate cancer assessment
December 14, 2015

1. ORD scientists have reviewed OPP's glyphosate cancer analysis and selection of cancer descriptor. The reviewers included two epidemiologists, a pathologist, and several scientists with significant expertise in cancer risk assessment. With the exception of one reviewer who participated in the recent IARC review and two reviewers who participated in the CARC review, an in-depth review of the original literature was not undertaken.

2. The goal of this focused, expedited review was to consider the characterization of glyphosate as "not likely to be carcinogenic to humans," given IARC's recent decision and looking at the totality of the available cancer database.

3. There are several epidemiological studies that vary in quality and study design. For many of the epidemiological studies, it appears that the small sample sizes limit their power to detect an outcome other than the null hypothesis. There are some epidemiological studies that show non-statistically significant elevated risks. One meta-analysis brings together those studies to strengthen the analysis and finds slightly elevated risks. The overall conclusion from IARC is that there is limited evidence of an association between glyphosate and non-Hodgkin's lymphoma (NHL). One major point is that a determination of causality is not what one would expect from most of the studies that are available given their design and power.

   ORD's epidemiologists agree with IARC that there is "limited evidence" of carcinogenicity in humans and understand IARC's definition of "limited evidence" as "a positive association has been observed" for which a causal association is "credible, but chance, bias, or confounding could not be ruled out with reasonable confidence [IARC Preamble, section B6]." OPP preferred to dichotomize the epidemiological evidence to be either "causal" or "not causal." This dichotomization appears to be the major factor in the different positions between OPP and IARC with regard to the epidemiological data.

   Frameworks for data analysis and causal determinations that are currently in use by EPA and the risk assessment community include gradations of causality. EPA's Cancer Guidelines utilizes these gradations to inform cancer descriptor choices. An example of situation where a less than causal determination is used is for the descriptor "likely to be carcinogenic to humans" – an agent demonstrating a plausible (but not causal) association between human exposure and cancer. The OPP draft risk assessment does not appear to follow these approaches. It would appear that OPP's use of a "yes/no" approach would only lead to cancer descriptors of "carcinogenic to humans" or "not likely to be carcinogenic to humans."

4. Glyphosate has been tested in a large number of 2-year rat and mice studies, including several studies conducted in the same strains. A wide range of tumors have been observed in these studies, including adenomas and some carcinomas. Tumors have been observed in thyroid, liver, skin, pancreas, hemangiosarcoma, lymph, testes, mammary glands, kidney and lung. However, the tumor incidences were generally not statistically significant in pair-wise comparisons and were generally within the range of historical controls. Most tumor types were only observed in one study despite repeat studies within the same strain and similar doses at or above the limit dose.

The tumors found in more than one study were in the pancreas and liver, and were observed in 2 of 4 studies in Sprague Dawley (SD) rats. A positive trend was found for male combined renal tubule adenomas and carcinomas in one CD-1 mouse study. This tumor is relatively rare in CD-1 mice. A positive trend was also found for hemangiosarcoma in males in another CD-1 mouse study. What makes the database so unusual is the large number of animal bioassays that have been conducted and the variety of types of tumors that have been observed, albeit usually at very low incidences. The OPP evaluation concluded that all of the tumors found were not treatment-related.

OPP (and EFSA) focus on pairwise comparisons (which were generally not significant), while IARC also uses trend tests, which yielded several significant results. In a few cases, OPP reported trend test results that differed from those of IARC but did not report which test they used. EPA's cancer guidelines state that "Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

5. The ORD reviewers noted that the analysis of the cancer data in the assessment was basically conducted on a study-by-study basis instead of using a more inclusive, systematic approach to provide an integrated analysis of the data. The cancer database for glyphosate is unusual. It is difficult to predict whether such an approach would yield a different outcome. It would likely be a large undertaking. A thorough evaluation of the mutagenic potential of glyphosate was not included in the assessment and was not conducted as a part of this review. This aspect of the assessment is important because if there is evidence of mutagenic potential or if a mutagenic potential has not been adequately ruled out, then characterization of glyphosate as "not likely to be carcinogenic" could be problematic for this reason alone, given the lack of a high-quality negative epidemiological study.

6. The main issue is whether the characterization of cancer potential for glyphosate as "not likely to be carcinogenic to humans" represents the best evaluation of the data. There are five EPA cancer guideline categories:
   - Carcinogenic to humans
   - Likely to be carcinogenic to humans
   - Suggestive evidence of carcinogenic potential
   - Inadequate information to assess carcinogenic potential
   - Not likely to be carcinogenic to humans

   According to the cancer guidelines, characterizing a chemical as either "carcinogenic to humans" or "not likely to be carcinogenic to humans" has a high bar with phrases such as "strong evidence" and "robust data" included in these descriptors. For glyphosate, nobody—including IARC—supports the top category (carcinogenic to humans). The descriptor "not likely to be carcinogenic to humans" is appropriate when "the available data are considered robust for deciding that there is no basis for human hazard concern." Examples include situations where there is "convincing evidence in both humans and animals that the agent is not carcinogenic" or animal evidence is available that "demonstrates a lack of carcinogenic effects in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects)."

"Likely to be carcinogenic" means that the "weight of the evidence is adequate to demonstrate carcinogenic potential to humans," giving as an example "an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments."

"Suggestive" evidence covers a spectrum of evidence ranging from "a positive cancer result in the only study on an agent to a single positive result in an extensive database that includes negative studies in other species." In ORD's experience, chemicals can fall into this category at the low end or the high end of the spectrum.

The descriptor "inadequate information to assess carcinogenic potential" is appropriate when "available data are judged inadequate for the other descriptors," and for which "additional studies would be expected to provide further insights." However, examples for when to use this descriptor range significantly from "little or no pertinent information," conflicting evidence (not to be confused with differing results, where "depending on the WOE, differing results can be considered either suggestive evidence or likely evidence)," to "negative results that are not sufficiently robust for not likely."

Summary: The ORD reviewers have not extensively discussed which descriptor might be most appropriate for glyphosate. In ORD discussions to date, "carcinogenic to humans" is clearly not applicable, and IARC and OPP are in agreement. One might classify glyphosate as "likely" on the basis of experimental data alone, by accepting positive trend tests at two anatomical sites (despite differing results in other studies) or by viewing these tumors (which not everyone accepts) as rare. One level down on the continuum puts you at "suggestive evidence." For this descriptor, one could argue that the evidence is not strong enough for the "likely" descriptor but it cannot be dismissed. The positive association (i.e., limited evidence) of carcinogenicity in humans could arguably rule out the last cancer category ("not likely to be carcinogenic"). One could also argue that this unusual data set is best suited to the descriptor "inadequate information to assess carcinogenic potential" based on an argument that the results are not sufficiently robust for the descriptor "not likely."

ORD Recommendation: To strengthen OPP's human health assessment and address the differences in the potential cancer findings, we recommend the following:

- Expand the discussion of the cancer data and subsequent findings to include a detailed and thorough discussion of the rationale that caused OPP to come to a different conclusion than IARC, if not directly noting the IARC findings themselves. Key controversies in how one could evaluate the data should be highlighted to provide transparency in how the Agency is making its determination. OPP could include a discussion of the strengths and weaknesses of choosing one cancer descriptor over the other.
- We understand that OPP plans to take the assessment to the SAP for external peer review. We recommend developing charge questions that will be specific to the cancer findings and ask the panel to address the specific scientific differences that exist between the IARC and OPP cancer determinations. ORD is willing to work with OPP to draft the charge questions, or review them before they are finalized.

EXHIBIT 16

To: Goodis, Michael[Goodis.Michael@epa.gov]
From: Rowland, Jess
Sent: Fri 5/22/2015 11:20:49 AM
Subject: RE: Bilateral EPA EFSA cooperation on pesticides

Hi

Yes; tell them it is "THE Just Remarkable"

Ru back or r u still sightseeing in Paris!!

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Goodis, Michael
Sent: Friday, May 22, 2015 7:19 AM
To: Rowland, Jess
Subject: Re: Bilateral EPA EFSA cooperation on pesticides

Jess

I was approached by EFSA about glyphosate. They are planning to issue a review including a cancer classification in Aug. They are saying they will disagree with IARC and will be more in line with us, and would like a point of contact within OPP as it leads up to that. Would that be you? I expect an email request for this in the coming days. Mike

---

From: Rowland, Jess
Sent: Tuesday, May 12, 2015 1:20:07 PM
To: Goodis, Michael
Subject: RE: Bilateral EPA EFSA cooperation on pesticides

Hi Mike

I don't have a summary of the IARC's conclusion other than the attached Lance publication which basically summarizes the IARC meeting conclusions.

I don't have any information on EFSA's position on glyphosate. I searched their web and did not locate any document on glyphosate carcinogenicity.

HED's CARC is scheduled to review all available epidemiological and animal data and IARC's decision logic on June 24th for inclusion into the July PRA.

Hope this helps

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Goodis, Michael
Sent: Monday, May 11, 2015 1:10 PM
To: Rowland, Jess
Subject: FW: Bilateral EPA EFSA cooperation on pesticides

Jess

See below…I've been asked to meet with EFSA to discuss a handful of items including the IARC classification for glyphosate.

EXHIBIT 17

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Wood, Charles[Wood.Charles@epa.gov]; Birchfield, Norman[Birchfield.Norman@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; McQueen, Jacqueline[McQueen.Jacqueline@epa.gov]
From: Flowers, Lynn
Sent: Tue 12/8/2015 9:57:16 PM
Subject: TRY THIS ONE! Glyphosate follow up
Glyphosate_Summary of ORD discussion_Dec 2015.docx

I got something screwed up and I think it is now fixed. Please ignore last version.

Lynn Flowers, PhD, DABT

Associate Director for Health

National Center for Environmental Assessment

US EPA

Washington, DC

703-347-8537

From: Cogliano, Vincent
Sent: Tuesday, December 08, 2015 4:27 PM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>
Cc: Wood, Charles <Wood.Charles@epa.gov>; Birchfield, Norman <Birchfield.Norman@epa.gov>; Lobdell, Danelle <Lobdell.Danelle@epa.gov>; McQueen, Jacqueline <McQueen.Jacqueline@epa.gov>
Subject: Re: Glyphosate follow up

Thanks, Lynn, for the additional text. For completeness, let's add the criteria for "Not likely." It's fundamental to understanding why some of us think a classification of "Not likely" is inappropriate.

Also, if the rationale for "Inadequate" is negative data that are not strong enough for "Not likely," then you've either dismissed the human studies or dichotomized their value to "not causal." The only way I see to get to "Inadequate" is that the positive human data are in conflict with the (largely) negative animal data.

Vince

On Dec 8, 2015, at 15:51, Flowers, Lynn <Flowers.Lynn@epa.gov> wrote:

Ok! I did some significant editing, thinking that what we needed was a complete 2 pager that Tom could provide to OPP based on Kacee's guidance.

I used Vince's draft and the comments from Danelle and Charles.

I have attached a redline but I would just read the clean copy if I were you. It got messy because I added a bunch of additional comments and statements around what Vince provided ☺.

See what you think.

Lynn

Lynn Flowers, PhD, DABT

Associate Director for Health

National Center for Environmental Assessment

US EPA

Washington, DC

703-347-8537

From: Wood, Charles
Sent: Monday, December 07, 2015 5:31 PM
To: Birchfield, Norman <Birchfield.Norman@epa.gov>; Lobdell, Danelle <Lobdell.Danelle@epa.gov>
Cc: Cogliano, Vincent <cogliano.vincent@epa.gov>; McQueen, Jacqueline <McQueen.Jacqueline@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>
Subject: RE: Glyphosate follow up

Hi Norm,

For point 6 (and perhaps 9), I would add 'Inadequate evidence' and 'Not likely to be carcinogenic' at the end to capture full range of opinions.

--Charles

From: Birchfield, Norman
Sent: Monday, December 07, 2015 12:44 PM
To: Wood, Charles <Wood.Charles@epa.gov>; Lobdell, Danelle <Lobdell.Danelle@epa.gov>
Cc: Cogliano, Vincent <cogliano.vincent@epa.gov>; McQueen, Jacqueline <McQueen.Jacqueline@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>
Subject: Fwd: Glyphosate follow up

Hi Charles and Danelle

Vince has summarized the perspectives expressed at our discussion with Tom a couple of weeks ago. Can you take a look and make sure you are okay with how he characterized things? I expect this write up will be transmitted to OPP.

From my perspective I think the write up could be more inclusive of the possibility of "inadequate information" due to conflicting results of studies.

Danelle - in paragraph 4 below, is the word "insisted" good? Would "OPP preferred to dichotomize the data" be better?

Thanks

Norm

Sent from my iPhone

Begin forwarded message:

> **From:** "Cogliano, Vincent" <cogliano.vincent@epa.gov>
> **Date:** December 7, 2015 at 12:01:11 PM EST
> **To:** "Birchfield, Norman" <Birchfield.Norman@epa.gov>
> **Subject: Re: Glyphosate follow up**

Hello Norm—Here are my thoughts on Kacee's second item below (ORD's conclusions under the cancer guidelines). The scientists who reviewed glyphosate materials didn't develop conclusions. If pressed, though, here's what I think might become a joint conclusion. It would be good to circulate this among the ORD scientists to get their views and edits ... Thanks!—Vince

Draft thoughts on glyphosate

1. There are five cancer guideline categories:

- Carcinogenic to humans

- Likely to be carcinogenic to humans

- Suggestive evidence of carcinogenic potential

- Inadequate information to assess carcinogenic potential

- Not likely to be carcinogenic to humans

2. Nobody—including IARC—supports the top category (Carcinogenic).

3. ORD's epidemiologists agree with IARC that there is "limited evidence" of carcinogenicity in humans. Our epidemiologists understand IARC's definition of "limited evidence" as "a positive association has been observed" for which a causal association is "credible, but chance, bias, or confounding could not be ruled out with reasonable confidence [IARC Preamble, section B6]." This positive association would rule out the last EPA category (Not likely to be carcinogenic).

4. At the ORD-only meeting you attended, you heard Danelle say that she tried to communicate this nuanced evaluation of the epidemiology, but that OPP insisted on dichotomizing this to be either "causal" or "not causal." This dichotomization is a major factor in the different positions.

5. Under the EPA's cancer guidelines, "Likely" means that the "weight of the evidence is adequate to demonstrate carcinogenic potential to humans," giving as an example "an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments."

6. I believe that ORD scientists would be split on whether there is adequate supporting experimental

evidence. Some might classify glyphosate as "Likely to be carcinogenic"; others, as "Suggestive evidence."

7. I also believe that some ORD scientists might classify glyphosate as "Likely" on the basis of experimental data alone, by accepting positive trend tests at two anatomical sites (despite differing results in other studies) or by viewing these tumors (which not everyone accepts) as rare.

8. The remaining EPA category (Inadequate information) has not been discussed within ORD, though the positive (albeit "limited") association in the human studies would seem to rule this out.

9. Bottom line: Based on glyphosate discussions to date among ORD scientists—where we have not formally discussed a classification—I believe we would be split between "Likely to be carcinogenic" and "Suggestive evidence."

From: McQueen, Jacqueline
Sent: Friday, December 04, 2015 7:49 AM
To: Cogliano, Vincent <cogliano.vincent@epa.gov>; Birchfield, Norman <Birchfield.Norman@epa.gov>
Cc: Fegley, Robert <Fegley.Robert@epa.gov>
Subject: Fw: Glyphosate follow up

Good morning. See below for the next steps on glyphosate. OPP is anxious to see ORD's specific comments, so they can begin working on them. Please take a look at Tom's action items below and let me know if the table is ready to share. Also, can you draft the short summary of ORD's conclusions, and provide the summary of the cancer guidelines that was used at the briefing for Tom?

We'd like to get these over to OPP as soon as possible. Once I get the materials from NCEA, we can circle back to make sure that Tom is ok with the the whole package.

Thanks in advance, and please let me know if we need to discuss.

Jackie McQueen

From: Deener, Kathleen
Sent: Thursday, December 3, 2015 5:45 PM
To: McQueen, Jacqueline
Cc: Hauchman, Fred; Fegley, Robert; Gwinn, Maureen; Bahadori, Tina
Subject: Glyphosate follow up

Hi Jackie –

Nice to run into you today in the food court! I talked with Tom about glyphosate, and here are the next steps:

- Review the four column chart and make sure it's good to send over to OCSPP (Tom wants them to have that, and he wants to use the 4-column version)

- Develop a one-pager that briefly (1-2 paragraphs) describes ORD's conclusions – including where we believe the cancer guidelines would lead us given this data set.

- At the meeting, Vince also had a hand-out of the cancer guideline categories. I can pull this from the Cancer Guidelines document, but it looks like he had a nice summary version. It would be great if NCEA would share that.

Thanks! Give me a call if you want to talk about any of this. I'll assume OSP will do the coordinating on this unless I hear otherwise from you.

Kacee Deener, MPH

Senior Science Advisor

Office of Research and Development

(ph) 202.564.1990 | (mobile) 202.510.1490

deener.kathleen@epa.gov

<Glyphosate_Summary of ORD discussion_Dec 2015_redline.docx>

<Glyphosate_Summary of ORD discussion_Dec 2015.docx>

EXHIBIT 18

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
(Proposition 65)

NOTICE TO INTERESTED PARTIES
JULY 7, 2017

CHEMICAL LISTED EFFECTIVE **JULY 7, 2017** AS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER: GLYPHOSATE

On March 28, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) posted a Notice on its website[1] that *glyphosate (CAS No. 1071-83-6)* would be added to the list of chemicals known to the state to cause cancer for purposes of Proposition 65[2] with a delayed effective date due to the pending case *Monsanto v OEHHA*.[3] Monsanto's challenge was unsuccessful in the trial court. Although the case has been appealed, no stay of the listing has been granted. Therefore, glyphosate is being added to the Proposition 65 list on July 7, 2017.

In summary, glyphosate is listed under Proposition 65 effective July 7, 2017 as known to the state to cause cancer, as follows:

Chemical	CAS No.	Endpoint	Listing Mechanism*
Glyphosate**	1071-83-6	Cancer	LC

*Listing mechanism: LC – "Labor Code" mechanism (Health and Safety Code section 25249.8(a) and Title 27 Cal. Code of Regs. section 25904)

** The International Agency for Research on Cancer (IARC) indicates the following chemicals are "also relevant: 38641-94-0 (glyphosate-isopropylamine salt) 40465-66-5 (monoammonium salt) 69254-40-6 (diammonium salt) 34494-03-6 (glyphosate-sodium) 81591-81-3 (glyphosate-trimesium)" (IARC, 2015b), because these salts dissociate to free glyphosate.

[1] The Notice was published in the California Notice Register on April 7, 2017.
[2] The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code section 25249.5 et seq.
[3] *Monsanto et al v OEHHA et al.*, Fifth District Court of Appeal, case number F075362.

EXHIBIT 19

FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: GLYPHOSATE

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL)[1] for glyphosate. On June 26, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) announced the listing of glyphosate, effective July 7, 2017, as a chemical known to the state to cause cancer for purposes of Proposition 65[2]. OEHHA issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 1100 micrograms per day (µg/day) for glyphosate under Title 27, California Code of Regulations, section 25705(b)[3]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation.

Briefly, in developing the NSRL for glyphosate, OEHHA relied on Volume 112 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos"[4], which summarizes the available data from rodent carcinogenicity studies of glyphosate, as well as other information relevant to the carcinogenic activity of this chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[5]. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in a study of male CD-1 mice is treatment-related and is using that study as the basis for the NSRL.

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[1] No Significant Risk Levels (NSRLs) for cancer-causing chemicals have been established for many of the chemicals listed under Proposition 65. A business would not be required to provide a Proposition 65 warning for an exposure to a listed carcinogen that is at or below the NSRL.

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq.*, hereafter referred to as "Proposition 65" or "The Act".

[3] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.

[4] International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

[5] Section 25703(a)(4)

The Notice of Proposed Rulemaking was published in the California Regulatory Notice Register on April 7, 2017 (Register 2017, No. 14-Z) and initiated a 45-day public comment period that was scheduled to close on May 22, 2017. OEHHA received several requests to extend the public comment period and it was extended until June 21, 2017. OEHHA received over 1,300 oral and written public comments on the proposed rulemaking from several organizations and numerous individuals.

PEER REVIEW

As required by Section 25302(e) of the regulations, on May 17, 2017, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed NSRL for glyphosate to the members of the Carcinogen Identification Committee for their individual review and comment. OEHHA received peer-review comments from committee members Thomas McDonald, M.P.H., Ph.D., Luoping Zhang, PhD, Shanaz Dairkee, PhD, and Jason Bush, Ph.D.

UPDATED INFORMATION

There are no updates to the information contained in the ISOR, and no new documents were relied upon or added to the rulemaking file. Non-substantive revisions were made to the final regulation text to align the text with the text currently printed in the California Code of Regulations.

SUMMARY AND RESPONSE TO RELEVANT COMMENTS RECEIVED

OEHHA's responses to the oral and written comments received throughout this rulemaking process are incorporated in this Final Statement of Reasons (FSOR). Some commenters analyzed IARC's scientific conclusions, supporting or disagreeing with IARC's classification of glyphosate as a Group 2A carcinogen and providing their own scientific analyses and conclusions, cited the conclusions of other international regulatory or scientific bodies that were contrary to IARC's, or expressed or reiterated general disagreement with the addition of glyphosate to the Proposition 65 list; such comments are not directed to the subject of this rulemaking, which is the establishment of an NSRL for glyphosate. OEHHA responded to these types of comments in the listing documents for glyphosate and does not respond to them again here.

Other commenters discussed the US Environmental Protection Agency's (US EPA's) report entitled 'Glyphosate Issue Paper: Evaluation of Carcinogenic Potential'[6],

[6] US EPA (2016). Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs, US Environmental Protection Agency. September 12, 2016. Available from: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

critiquing the analysis and conclusions therein, including comments that US EPA did not follow good laboratory practices in its weight of the evidence evaluation by omitting relevant studies[7], as well as concerns that the cancer-related data provided by the US EPA has been brought into question based on allegations of collusion with Monsanto. These comments are not directed to the subject of this rulemaking and are not responded to here.

OEHHA additionally received many comments during the regulatory process that included observations or opinions regarding the use of glyphosate; suggestions that OEHHA conduct further studies into the health effects of glyphosate; statements that the NSRL does not consider impacts other than carcinogenicity; concerns of increased chronic illness among children and the lack of studies of the effects of pesticides on children[8]; opinions that glyphosate is safe, regulated, and effective; statements of support for other actions that are not the subject of this rulemaking (such as banning or restricting use of the chemical); and recommendations to use methods of clinical testing of 0.5 parts per billion or lower, and much lower for urine and water testing[9]. Some commenters expressed concern over the negative effects of genetically modified organisms (GMOs), that all GMOs should be banned, or that the US Food and Drug Administration should adopt mandatory regulations concerning genetically engineered plants and animals[10]. Some commenters also stated that Monsanto is greedy, corrupt, or withholding scientific evidence of glyphosate's toxicity to humans and animals[11]. Such remarks do not constitute an objection or recommendation specifically directed at the proposed action, or the procedures followed in this rulemaking action. Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[12], OEHHA does not provide responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA agrees with them.

Many commenters made the same or similar comments, and this document does not provide an exhaustive accounting of all commenters addressing the same point. A summary of the comments relevant to this rulemaking is provided below, along with OEHHA's responses to those comments. As explained in detail in the responses to comments, OEHHA declines to change the proposed NSRL based on the comments.

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[7] Comment from Kurt Wallace.
[8] Comment from Michelle Perro
[9] Comment from Diane Rude
[10] Comment from Stephanie Easton
[11] Comment from Kathleen Furey
[12] California Government Code section 11346.9(a)(3)

Comment 1 (Baum, Hedlund, Aristei & Goldman, P.C., A Voice for Choice, Donna R. Farmer, Ph.D., on behalf of Monsanto and others): The potency estimate for the NSRL should be based on cancer findings from human epidemiological studies, rather than on findings from animal carcinogenicity studies. Many commenters assert that in failing to consider epidemiologic studies, the proposed safe harbor level does not conform to "quantitative risk assessment" and that OEHHA did not follow Section 25703 of the regulations.

Some of these commenters went on to state that prioritizing animal bioassays over epidemiological data overlooks the risk to individuals exposed to glyphosate during its application as a pesticide. They further argue that use of epidemiological data would provide a more robust and comprehensive evaluation of a chemical which most users absorb via cutaneous and respirational contact.

Paul Eusey, Tricia Brooks, and several other commenters stated that OEHHA should review the lowest levels of glyphosate in the epidemiological studies, but should always err on the side of caution and public health (see also Response #29 and discussion of precautionary principle).

Response 1: As stated in Section 25703 of the regulations, the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[13]. Glyphosate was listed pursuant to the Labor Code listing mechanism[14] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of sufficient evidence of carcinogenicity in experimental animals[15,16]. IARC also found "there is *limited evidence* in humans for the carcinogenicity of glyphosate", noting "[a] positive association has been observed for non-Hodgkin lymphoma." Given that the listing of glyphosate is based on findings of limited evidence in humans and sufficient evidence in animals, basing the potency estimate for the NSRL on animal studies is both appropriate and consistent with Section 25703.

Animal bioassays are more frequently used than epidemiological data in quantitatively assessing the health risks of chemicals, including carcinogens. The epidemiological

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[13] Section 25703(a)(4)
[14] Section 25249.8(a) of the Act
[15] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[16] IARC (2015). Full citation provided in footnote 3.

studies evaluated by IARC, like many human studies, do not provide the type of information on levels of exposure that is needed for dose-response analysis. Specifically, these studies broadly characterized glyphosate exposure to individuals as either 'never' or 'ever' exposed, or as 'duration' of exposure, and were unable to quantify the individuals' specific levels of exposure to the chemical. Since the epidemiology studies did not measure or estimate the dose level to which participants were exposed, a cancer potency cannot be calculated using these studies.

OEHHA disagrees with the commenters' assertions that the use of animal cancer bioassay data to estimate cancer potency results in a less robust or comprehensive risk assessment than would the use of epidemiologic data, or that the use of animal data in some way overlooks risks to workers or other individuals exposed to glyphosate. As noted above, the epidemiologic studies available to date on glyphosate only provide limited evidence of a causal relationship between exposure and cancer risk, and they do not provide the type of information on levels of exposure needed in order to estimate cancer potency. Thus, OEHHA's use of animal cancer bioassay data from the most sensitive study of sufficient quality to estimate human cancer potency for this chemical is appropriate and consistent with the Proposition 65 regulations[17], other cancer risk assessment guidance from OEHHA[18], and guidance from US EPA[19]. The estimate of human cancer potency is equally valid for estimating risks to occupationally exposed workers and to other individuals exposed to glyphosate, and the NSRL for glyphosate is not limited to a specific route of exposure[20,21]. No change to the regulatory proposal was made based on these comments.

Comment 2 (Moms Across America, Marty Eustis, Majorie Golden, Gloria Anderson and other commenters): Glyphosate induces breast cancer in humans. Marty Eustis commented that the NSRL should be "substantially lower" than the proposed 1100 micrograms/day in order to actually be safe to Californians. Majorie Golden, Gloria Anderson, and Marty Eustis commented that until a comprehensive independent study is done, the NSRL should be at or "well below 0.0001 mg/day" (Thongprakisang et al.), the concentration where it stimulated breast cancer cells in vitro.

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[17] Section 25703

[18] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[19] US EPA (2005). Guidelines for Carcinogen Risk Assessment. March, 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[20] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[21] Section 25703(a)(4)

Response 2: These comments all appear to be based on an *in vitro* study by Thongprakaisang et al. (2013)[22], in which glyphosate was shown to induce proliferation in a hormone-dependent human breast cancer cell line (T47D cells derived from ductal carcinoma cells), but not in a hormone-independent human breast cancer cell line (MDA-MB231 breast adenocarcinoma cells). This study is not a human epidemiology study and thus it does not provide evidence that glyphosate induces breast cancer in humans. Rather, it is a study of the effect of glyphosate on the proliferation of cultured cells, and it does not provide information that can be used to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

Comment 3 (Monsanto, Ramboll Environ on behalf of The Scotts Company LLC, and others): Reviews by others have concluded that there are no treatment-related tumors in animal cancer bioassays of glyphosate, nor are there other datasets that provide evidence of a strong dose-response relationship of carcinogenicity that could be relied upon to estimate the potential for health effects in humans following exposure to expected concentrations and that the lack of an adequate dataset is consistent with conclusions reached by JMPR (2006) and US EPA (2016) that any tumor findings are not treatment-related. OEHHA has no basis to quantify an NSRL using experimental animal studies.

Response 3: Glyphosate was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's classification[23] of glyphosate as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for glyphosate. IARC's conclusion of sufficient evidence in experimental animals is based on findings from two studies in male mice. Specifically, IARC cited "a significant positive trend in the incidence of haemangiosarcoma [a malignant neoplasm] in male CD-1 mice" in a two-year diet study[24], and "a positive trend in the incidence of renal tubule carcinoma [a malignant neoplasm] and of renal tubule adenoma and carcinoma (combined) [an appropriate combination of benign and malignant neoplasms]" in male CD-1 mice in a different

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[22] Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J., 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. *Food Chem Toxicol* **59**:129-36.
[23] IARC (2015). Full citation provided in footnote 3.
[24] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

two-year diet study[25], with IARC noting that these malignant kidney tumors are rare in this strain of mice. OEHHA agrees with IARC's determination that these tumor findings are treatment-related and demonstrate statistically significant dose-response relationships.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet, in which a significant positive trend in the incidence of hemangiosarcomas was observed, met the criteria in 25703 as the most sensitive study of sufficient quality. OEHHA used this data to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

Comment 4 (Monsanto): The commenter cited the decision in *Baxter Healthcare Corp. v. Denton,* 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004) to support its assertion that OEHHA is required to determine that a glyphosate exposure at any level does not pose a "significant risk", and as such requires OEHHA to establish an "infinite" NSRL. Baum, Hedlund, Aristei & Goldman, P.C. and others stated that Monsanto's reliance on *Baxter v. Denton* is inappropriate.

Response 4: OEHHA disagrees that the *Baxter* decision mandates the establishment of an infinite NSRL. The decision in *Baxter* is factually distinguishable from the proposed NSRL for glyphosate[26]. The commenter provides no evidence that the mechanism of action for glyphosate does not operate in humans, which was the pivotal issue in that case. In *Baxter*, the Appellate Court focused on evidence that the mechanism by which DEHP increased the incidence of liver tumors in animals was not relevant to humans[27]. This notably included evidence regarding the classification of DEHP by IARC[28]. At the time of the *Baxter* decision, IARC had downgraded its earlier classification of DEHP as Group 2B ("possibly carcinogenic to humans") to Group 3 ("not classifiable as to its carcinogenicity to humans"). Glyphosate, on the other hand,

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[25] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).
[26] See comment letters from Baum, Hedlund, Aristei & Goldman, P.C., (Comment #9945) and Center for Biological Diversity, et al. (Comment #9974)]
[27] Baxter Healthcare Corp. v. Denton, 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004), at 438.
[28] *Id.*

has received a higher Group 2A classification from IARC[29]. IARC's Group 2A classification of glyphosate is based on "sufficient evidence" in animal studies and "limited evidence" in human (epidemiological) studies. IARC found that mechanistic and other relevant data support the Group 2A classification of glyphosate (e.g., "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations) and concluded, "[t]here is evidence that these effects can operate in humans". IARC has not reclassified glyphosate, or modified its findings that animal studies provided sufficient evidence of carcinogenicity and human studies provided limited evidence of carcinogenicity. No changes to the regulatory proposal were made based on this comment.

Comment 5 (Monsanto, Chris Portier, SafeAgSafeSchools, Anthony Samsel, Baum, Hedlund, Aristei & Goldman, P.C., and others): Monsanto commented that according to Section 25703, OEHHA's assessment is not limited to the specific studies used as the basis for listing the chemical, but instead OEHHA's "assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer." Monsanto went on to say that OEHHA's basis for listing is IARC's classification of glyphosate as a category 2A chemical on the basis of sufficient evidence in animals and that OEHHA should consider all available rodent studies and not just the select few that IARC chose to evaluate. The other studies contradict the conclusions reached by IARC's working group with respect to the four referenced animal studies.

Additionally, Chris Portier, Safe Ag Safe Schools, Anthony Samsel, Baum, Hedlund, Aristei & Goldman, P.C., Sonoma County Conservation Action[30] and others requested that OEHHA analyze and incorporate additional bioassay data in the derivation of an NSRL for glyphosate, not just studies reviewed by IARC. This includes the studies discussed in the review article by Greim et al. (2015). Some of these studies, including Wood et al. (2009), Lankas (1981), and Stout and Ruecker (1990), as cited by Baum, Hedlund, Aristei & Goldman, P.C. and Safe Ag Safe Schools, observed tumors or lymphomas at much lower doses than the study used to derive the NSRL. Baum, Hedlund, Aristei & Goldman, P.C, stated that if the data from these studies were used, a significantly lower NSRL would have been reached. Safe Ag Safe Schools stated that the NSRL is not based on the most sensitive study of acceptable quality and should be based on a dose of 31.49 mg/kg/day. Chris Portier and the Center for Biological Diversity commented that the Atkinson study is not the most sensitive study of sufficient

[29] IARC (2015). Full citation provided in footnote 3.
[30] The commenter suggested a revised NSRL based on a dose of 31.39/mg/kg/day, which is related to the Lankas study discussed in Greim et al.

quality to guide the suggested NSRL, and that other studies provide a more scientifically sound and health- protective basis for calculating the NSRL (i.e., Wood et al. [2009], Lankas [1981], and Stout and Ruecker [1990]), and that OEHHA must do an independent analysis of these studies and not rely on US EPA's conclusions.

During the public hearing for this rulemaking, Dr. Donna Farmer, senior toxicologist at Monsanto's Regulatory Product Safety Center, commented that OEHHA's reliance on male mouse hemangiosarcomas is not justified for the derivation of a NSRL.

Seosamh Devine commented that OEHHA relied too much on Monsanto's scientific opinions.

Response 5: As noted by the commenters, Section 25703 of the regulations states that the assessment used to derive the cancer potency "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[31]. Glyphosate was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's classification[32] of glyphosate as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for glyphosate. As discussed in response to comment 3, IARC's conclusion of sufficient evidence in experimental animals is based on findings from two studies in male mice. Specifically, IARC cited "a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice" in a two-year diet study[33], and "a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma and carcinoma (combined)" in male CD-1 mice in a different two-year diet study[34], with IARC noting that these malignant kidney tumors are rare in this strain of mice.

In contrast to the commenters implication that IARC only evaluated a select few studies in its monograph on glyphosate, IARC[35] discussed each of the 14 sets of animal cancer

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[31] Section 25703(a)(4)

[32] IARC (2015). Full citation provided in footnote 3.

[33] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[34] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[35] IARC (2015). Full citation provided in footnote 3

studies (five in mice and nine in rats)[36] included in the review by Greim *et al.* (2015)[37], as well as two additional sets of studies in rats, for a total of 16 sets of animal cancer studies. IARC noted in particular that the information reported in the article by Greim *et al.* and provided in the supplemental materials lacked sufficient detail regarding "statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture" to be evaluated[38]. IARC evaluations "rely only on data that are in the public domain and available for independent scientific review"[39]. Utilizing additional sources in the public domain, IARC was able to conduct independent scientific review of two of the five sets of mouse studies included in Greim *et al.*, five of the nine sets of rat studies included in Greim *et al.*, and two additional sets of rat studies not included in Greim *et al.*

OEHHA is not aware of any additional animal cancer studies of glyphosate, other than the 16 sets of studies discussed by IARC. Of those 16 sets, IARC found that two sets of studies in mice and six sets of studies in rats were *adequate* for the evaluation of glyphosate carcinogenicity (emphasis added).

Of those eight sets of rodent studies, treatment-related increases in the incidence of malignant tumors were observed in one study in male mice, and treatment-related increases in the incidence of combined malignant and benign tumors were observed in a second male mouse study. Treatment-related increases in benign tumors were observed in two male rat studies and one female rat study; in each case, IARC noted there was no apparent progression of the benign tumors to malignancy.

Thus, OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate in light of the requirement of Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met the criterion in Section 25703 as the most sensitive study of sufficient quality. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

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[36] Each set of studies consists of two experiments, one in males and one in females.

[37] Greim H, Saltmiras D, Mostert V, Strupp C (2015). Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit Rev Toxicol* 45(3):185-208.

[38] IARC (2015). Full citation provided in footnote 3.

[39] IARC (2015). IARC monograph Volume 112, General Remarks. p. 35.

OEHHA used this data to derive the NSRL for glyphosate. OEHHA did not rely on US EPA's conclusions to derive the NSRL for glyphosate; nor did OEHHA rely on Monsanto's scientific opinions to derive the NSRL (see also Response #3).

No changes were made to the regulatory proposal based on this comment.

Comment 6 (Valerie Noble and several commenters): The proposed NSRL does not account for bioaccumulation of glyphosate. Food Democracy Now further stated that a 2004 joint report from the United Nations Food and Agriculture [Organization] Program [*sic*] and the World Health Organization determined that glyphosate accumulates in the bones of lab animals.

Response 6: Valerie Noble did not provide a citation for the finding she attributed to Kruger et al. regarding bioaccumulation of glyphosate. OEHHA performed a literature search and identified one publication authored by Monika Kruger[40] . Contrary to the commenter's assertion, this publication provides no data indicating that glyphosate bioaccumulates. OEHHA is not aware of any evidence from studies in humans that demonstrate that glyphosate bioaccumulates. Similarly, there is no evidence that glyphosate bioaccumulates in non-human primates, or other mammals. For example, in rhesus monkeys, nearly all of an intravenous dose of glyphosate was eliminated within 24 hours[41], and in Fischer 344 rats greater than 90% of an oral dose of glyphosate was eliminated within 72 hours[42]. In another rat study, the total body burden of radiolabeled glyphosate residues measured 7 days after a single oral dose was approximately 1% of the administered dose. Further, no evidence of glyphosate bioaccumulation was observed in two repeated dosing studies conducted in rats[43].

The report referred to by the commenters appears to be the 2006 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) report. However, the report does not conclude that glyphosate accumulates in the bones of lab animals. The report states that, after reviewing studies in mammals, there is no evidence of accumulation of glyphosate in

[40] Krüger M, Shehata AA, Schrödl W, and Rodloff A (2013). Glyphosate suppresses the antagonistic effect of Enterococcus spp. on Clostridium botulinum. Anaerobe 20: 74–78. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23396248
[41] IARC (2015) p. 45, full citation provided in footnote 3.
[42] IARC (2015) p. 44, full citation provided in footnote 3.
[43] IARC (2015) p. 43, full citation provided in footnote 3.

mammals[44][45]. No changes were made to the regulatory proposal based on this comment.

Comment 7 (Meghan Lawler, Pesticide Free Zone, and Laura Hayes, Linda Causey, Zen Honeycutt and other commenters): OEHHA should consider effects other than carcinogenicity in setting the NSRL, such as evidence of induction of liver disease at 4 nanograms/kg, teratogenicity, breakdown of the blood-brain barrier, and evidence of destruction of gut bacteria at 0.1 ppm. Meghan Lawler and Laura Hayes stated that glyphosate is a neurotoxin, endocrine disruptor, mineral chelator, and antibiotic, and that it causes liver disease.

Some commenters stated that the NSRL fails to account for the potential transgenerational effects of endocrine disruptors, and asserted that an appropriate study to determine the NSRL should involve mice studies for three generations. Pesticide Free Zone commented that by excluding low dose studies from consideration, OEHHA may not be accounting for harmful endocrine-disrupting chemical actions. Laura Hayes commented that the most serious negative health consequences result when glyphosate substitutes for glycine during protein synthesis.

Response 7: Proposition 65 requires the maintenance and updating of a list of chemicals that cause cancer or reproductive toxicity, and requires businesses that knowingly cause exposures to listed chemicals to provide warnings. Other health effects – including liver disease, breakdown of the blood-brain barrier and destruction of gut bacteria – are outside the scope of the law. Following the guidance set forth in Section 25703, OEHHA bases NSRLs on cancer dose-response assessments, which are conducted using data from the most sensitive scientific studies deemed to be of sufficient quality. Observations of liver disease, teratogenicity, breakdown of the blood-brain barrier, destruction of gut bacteria, and endocrine disruption are not observations of cancer, and thus studies relating to such health effects do not provide data that can be used in a cancer dose-response assessment. The NSRL for glyphosate is based on animal carcinogenicity studies, and dose-response analysis of tumor incidence data from these studies.

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[44] JMPR (2006). Glyphosate. In: Pesticide residues in food – 2004. Evaluations 2004 Part II – Toxicological evaluations, Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group, Rome, Italy, 20-29 September 2004, p. 95–116, 172. Available from: whqlibdoc.who.int/publications/2006/9241665203_eng.pdf

[45] JMPR (2016). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues, Geneva, 9 to 13 May 2016. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO) (FAO Plant Production and Protection Paper No. 227), p. 19–28, 45, 72–82. Available from: http://www.fao.org/3/a-i5693e.pdf

In reviewing the mechanistic data available for glyphosate, IARC did not conclude that glyphosate is carcinogenic via endocrine disruption. Rather, IARC concluded that there was strong evidence for genotoxicity and oxidative stress, and weak evidence for receptor-mediated effects. There are no data to suggest that glyphosate acts as a carcinogen via a transgenerational mechanism. OEHHA is not aware of any multi-generational cancer studies of glyphosate.

No changes were made to the regulatory proposal based on these comments.

Comment 8 (K. Paul Stoller, MD, Nancy O'Mara, MPH, Mei-Ling Stefan, Anthony Samsel and others): Urge consideration of the possible human health effects of other chemicals present in commercial formulations of glyphosate, e.g. adjuvants, surfactants, and inert ingredients, as well as consideration of possible synergism of glyphosate with other xenobiotic chemicals. There are no safe levels of the N-nitrosamines of glyphosate that are found in every glyphosate product.

Response 8: The Proposition 65 warning requirement applies only to chemicals listed for causing cancer or reproductive toxicity. In this case, the substance listed as causing cancer is glyphosate[46], not commercial formulations of glyphosate. Analysis of possible effects (*e.g.,* additive, synergistic, or antagonistic) of other exposures that may co-occur with glyphosate is outside the scope of Proposition 65 and is not relevant to the derivation of the NSRL for glyphosate. Thus, the NSRL is based on the results of the most sensitive scientific study of *glyphosate* deemed to be of sufficient quality. No changes were made to the regulatory proposal based on this comment.

Comment 9 (Dr. Stephen C. Frantz, Nancy O'Mara, MPH, and others): Urge consideration of a non-linear dose-response relationship, stating that endocrine disrupting chemicals, such as glyphosate, do not demonstrate the common default monotonic dose-response relationship.

Response 9: No data were provided to support the assertions that a non-monotonic cancer dose-response relationship exists for glyphosate.

[46] As noted in the Notice of Intent to List Glyphosate (https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-tetrachlorvinphos-parathion-malathion-glyphosate) and the Notice of Listing (https://oehha.ca.gov/proposition-65/crnr/glyphosate-listed-effective-july-7-2017-known-state-california-cause-cancer), the 2015 IARC monograph on glyphosate indicates the following chemicals are "also relevant: 38641-94-0 (glyphosate-isopropylamine salt) 40465-66-5 (monoammonium salt) 69254-40-6 (diammonium salt) 34494-03-6 (glyphosate-sodium) 81591-81-3 (glyphosate-trimesium)" (IARC, 2015b), because these salts dissociate to free glyphosate.

As discussed in the Initial Statement of Reasons (ISOR)[47] for this action, OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC and determined that the most sensitive scientific study of sufficient quality for the cancer dose-response assessment was a study in male mice in which a statistically significant increasing trend in hemangiosarcoma was observed. The data from this study exhibited a monotonic dose-response relationship. Based upon consideration of the available mechanistic and other relevant data, OEHHA fit a multistage polynomial cancer model to the dose-response data to estimate cancer potency and derive the NSRL for glyphosate. This is consistent with the guidance set forth in Section 25703. No changes were made to the regulatory proposal based on this comment.

Comment 10 (Anthony Samsel): Glyphosate is a synthetic amino acid and an analogue of glycine. Glyphosate ligates with lysozyme, which may impact fibrocystic cytokines and human and animal immune systems. Glyphosate inhibits several enzymes, including protease, lipase, and pepsins, which can have effects on human health.

The commenter submitted three publications that were not included in IARC's review (Table 1).

Response 10: This comment is essentially a summary of Samsel and Seneff's 2016 article, entitled "Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins"[48]. This paper proposes a number of hypotheses regarding possible mechanisms by which glyphosate may effect human health. However, these hypotheses are not supported by experimental data and the relevance of the hypothesized health effects to cancer induction is unclear.

OEHHA reviewed each of the three publications in the context of the guidance set forth in Section 25703, which provides that "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[49] and determined that none of the studies provide data that would affect the cancer dose-response analysis (See Table 1). No changes were made to the regulation based on this comment.

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[47] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[48] Samsel A and Seneff S (2016). Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins. *J Biol Phys Chem* **16**:9-46.

[49] Section 25703(a)(4)

Table 1. Publications submitted by Anthony Samsel

Reference	Comments
Samsel A and Seneff S (2015). Glyphosate pathways to modern disease IV: Cancer and related pathologies. *Journal of Biological Physics and Chemistry* **15**:121-159.	This article reviews epidemiological evidence of cancers in humans exposed to glyphosate and mechanistic information on glyphosate, and discusses possible carcinogenic mechanisms. "Glyphosate has a large number of tumorigenic effects on biological systems, including direct damage to DNA in sensitive cells, disruption of glycine homeostasis, succinate dehydrogenase inhibition, chelation of manganese, modification to more carcinogenic molecules such as N-nitrosoglyphosate and glyoxylate, disruption of fructose metabolism, etc." This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Samsel A and Seneff S (2016). Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins. *Journal of Biological Physics and Chemistry* **16**:9-46.	This article proposes that glyphosate is a synthetic amino acid and analogue of glycine, which can be incorporated into peptides, affect various enzymes, and lead to numerous diseases. "Glyphosate, acting as a glycine analogue, may be mistakenly incorporated into peptides during protein synthesis." "…the combination of activation of kinases and suppression of phosphatases that can plausibly be induced through glyphosate's displacement of conserved glycines in the enzymes can be predicted to lead to an overabundance of phosphorylated molecules, systemically." "Phosphorylation is a widespread modification with profound effects on affected molecules, which can increase risk to both Alzheimer's disease and cancer."

	"VLA-4 [very late antigen-4] is required for normal development of both T- and B-cells in the bone marrow, in part by regulating the balance between proliferation and differentiation of haematopoietic progenitors [291]. It can therefore be expected that impaired function would lead to pathologies such as immune dysfunction and cancer. Two conserved glycine residues at positions 130 and 190 are essential for its adhesive activity [292]. Glyphosate's link to NHL may therefore be explained through substitution of glyphosate for glycine at one or both of these conserved residues." This paper proposes a number of theories regarding disease mechanisms. However, these theories are not supported by experimental data. This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Samsel A and Seneff S (2017). Glyphosate pathways to modern disease VI: Prions, amyloidoses and autoimmune neurological diseases. *Journal of Biological Physics and Chemistry* **17**:8-32.	This article is a review of glyphosate and autism, multiple sclerosis, and other autoimmune disorders. The only reference to cancer is the reporting of a correlation between the incidence of thyroid cancer in the US and an increase in glyphosate usage on corn and soy crops. However, statistical correlations of cancer incidence with usage/exposure are not enough to presume causation. This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.

Comment 11 (Dr. Stephen C. Frantz): "Developing an NSRL that relies on 'acceptable calculated reference doses' supplied by the USEPA and its international counterparts is generally troublesome. That is, the EU 'standard' for daily chronic exposure to [glyphosate] is 0.5 mg/kg body weight, a level that is 3.5 fold *lower* than the U.S. 'standard' of 1.75 mg/kg body weight. Obviously, both levels cannot be acceptable and safe; and the EU version is already less than half of the proposed 1.1 mg by OEHHA."

Response 11: The NSRL for glyphosate does not rely on "acceptable calculated reference doses" or other values calculated by other agencies. Following the guidance

set forth in Section 25703, NSRLs are based on cancer dose-response assessments, which are conducted using data from the most sensitive scientific studies deemed to be of sufficient quality. As discussed in the ISOR for this rulemaking[50], OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met this criterion. OEHHA used this data to derive the NSRL for glyphosate.

Furthermore, as stated in Section 25703, an NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question." NSRLs are intended to aid businesses in determining if they must comply with the warning and discharge provisions of Proposition 65; NRSLs are not intended to establish exposure or risk levels for other regulatory purposes (Section 25701(d)).

While reference doses set by other agencies are not relevant to this rulemaking, OEHHA notes that the European Union has set the *acceptable daily intake* (ADI) for glyphosate at 0.5 mg/kg[51], and US EPA has set the *chronic reference dose* (cRfD) for glyphosate at 1.00 mg/kg-day[52]; each of these values was developed by applying an uncertainty factor to a No Observed Adverse Effect Level (NOAEL) derived from developmental toxicity studies in rabbits. Neither value was based on cancer dose-response assessment and neither was developed specifically to protect against cancer. And finally, the ADI set by the European Union is not less than half of the proposed NSRL for glyphosate. The NSRL is expressed as an intake of µg/day, while the ADI (and cRfD) are expressed as mg/kg-day. Normalized to body weight, the NSRL would be less than the ADI or cRfD, not greater. No changes were made to the regulatory proposal based on this comment.

Comment 12 (The California League of Food Processors): Establishing an NSRL conflicts with tolerances set by US EPA for residues in food.

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[50] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[51] European Food Safety Authority (EFSA, 2015). Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015;13 (11):4302. doi:10.2903/j.efsa.2015.4302. Available from: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4302/epdf, page 13

[52] The commenter refers to the former cRfD set by US EPA. The value has been updated since the comment was submitted, as shown in US EPA (2017). Glyphosate. Dietary Exposure Analysis in Support of Registration Review. Office of Chemical Safety and Pollution Prevention. Available from: https://www.epa.gov/sites/production/files/2017-12/documents/glyphosate_dietary_exposure_analysis_in_support_of_registration_review.pdf

Response 12: There is no direct correlation between a tolerance level set by US EPA and an NSRL adopted for purposes of Proposition 65. The two standards are developed under different laws and have different purposes. Whereas tolerances are mandatory maximum allowable pesticide residues on foods, NSRLs identify levels of exposure to listed carcinogens associated with a 1 in 100,000 cancer risk. If a food exposure to a pesticide listed as a carcinogen results in a cancer risk greater than 1 in 100,000, Proposition 65 requires a warning even if the food complies with US EPA's tolerances and can be legally sold in California. In such an instance, Proposition 65 gives Californians the right to be informed of the exposure and to make their own decision as to whether they wish to purchase or consume the food. No changes were made to the regulatory proposal based on this comment.

Comment 13 (K. Paul Stoller, MD): Regulators should not rely on just one study to determine acceptable daily intake.

Response 13: No Significant Risk Levels (NSRLs) are distinct from Acceptable Daily Intakes (ADIs). The NSRL is defined in the Proposition 65 regulations as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question." ADI values, on the other hand, are based on non-cancer health effects, and are neither defined nor used under Proposition 65.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. No changes were made to the regulatory proposal based on this comment.

Comment 14 (Anthony Samsel): A thorough consideration cannot be had without a deep investigation and understanding of the nitrosamines of glyphosate which are carcinogens.

Response 14: Nitrosamines of glyphosate are not listed under Proposition 65 as causing cancer, nor are they the subject of this rulemaking. As discussed in response to comment 8, an NSRL applies specifically to the particular substance or chemical that has been listed as known to the state to cause cancer[53]. Therefore, studies of other chemicals, such as nitrosamines of glyphosate, do not provide information relevant to the derivation of the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

[53] Health and Safety Code section 25249.10(c) and Title 27, Cal. Code of Regs. section 25701.

Comment 15 (Ramboll Environ, on behalf of The Scotts Company, LLC): OEHHA and IARC failed to consider additional conclusions from the 2006 JMPR report on the study used to derive the NSRL, namely the lack of a dose-response relationship, the lack of statistically significant comparisons between treated animals and control animals, and the fact that the incidences were within the historical ranges for controls, and thus improperly reached conclusions regarding use of this data. Dr. Thomas McDonald, a peer reviewer and member of the Carcinogen Identification Committee, also stated that the dataset selected as the basis for the NSRL does not appear to be well supported as a treatment-related effect.

Response 15: As discussed in response to comment 5, IARC conducted an independent scientific review of the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet, which OEHHA used to derive the NSRL. IARC concluded that a treatment-related increase in hemangiosarcomas was observed in this study, with a statistically significant positive trend. The tumor incidence data and positive trend test results, shown in Table 1 of the ISOR[54], demonstrate the dose-response relationship observed for hemangiosarcoma in this study.

While the pairwise comparison between the tumor incidence in animals in the high dose group and those in the control group did not rise to the $p < 0.05$ level of statistical significance, data from Charles River Laboratories indicate that hemangiosarcomas are infrequently observed in untreated male CD-1 mice, with a mean incidence of 1.13% (range 0% – 12.00%) reported in 2000[55], and 0.56% (range 0% - 4.55%) in 2010[56]. More specifically, no hemangiosarcomas were observed in untreated controls in 38 of the 46 studies summarized in 2000[57], or in 13 of the 14 studies summarized in 2010[58].

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[54] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[55] Giknis MLA and Clifford CB (2000). Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse. Charles River Laboratories, Wilmington, MA.

[56] Giknis MLA and Clifford CB (2010). Spontaneous Neoplastic Lesions in the Crl:CD1 (ICR) Mouse in Control Groups from 18 Month to 2 Year Studies. Charles River Laboratories, Wilmington, MA. Available from: http://animalab.eu/sites/all/pliki/produkty-dopobrania/spontaneous-neoplastic-lesions-in-the-crlcd1icr-mouse-in-control-groups-from-18-month-to-2-year-studies-march-2010.pdf

[57] Giknis MLA and Clifford CB (2000). Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse. Charles River Laboratories, Wilmington, MA.

[58] Giknis MLA and Clifford CB (2010). Spontaneous Neoplastic Lesions in the Crl:CD1 (ICR) Mouse in Control Groups from 18 Month to 2 Year Studies. Charles River Laboratories, Wilmington, MA. Available from: http://animalab.eu/sites/all/pliki/produkty-dopobrania/spontaneous-neoplastic-lesions-in-the-crlcd1icr-mouse-in-control-groups-from-18-month-to-2-year-studies-march-2010.pdf

While JMPR[59] stated that the tumor "incidences recorded in this study fell within the historical ranges for controls", OEHHA notes, "concurrent controls are considered the most relevant comparison group for evaluating potential exposure-related tumor effects"[60]. In discussing the use of historical control data, IARC states "less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. 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, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment"[61].

OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

No changes were made based on this comment.

Comment 16: (Ramboll Environ, on behalf of The Scotts Company, LLC): The data used to derive the NSRL does not establish consistency across studies that is needed to provide a causal connection between exposure to glyphosate and cancer: there was no dose-related incidence of hemangiosarcoma reported in the female mouse study and no statistically significant increases in any tumors in another study with comparable concentrations.

Response 16: Section 25703(1) specifies that animal cancer bioassays must meet generally accepted scientific principles (e.g., the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence) in order to be used in the development of NSRLs. In carcinogenicity testing there is no requirement or expectation that the same tumors will be seen in male and female animals of the same species and strain. It is also recognized that differences in study design (*e.g.*, doses tested; length of exposure; length of study) and implementation (*e.g.*, test substance purity/composition/lot; animal strain/substrain/colony/supplier of

[59] JMPR (2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169

[60] National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. Office of the Report on Carcinogens, Division of the NTP, National Institute of Environmental Health Sciences, US Department of Health and Human Services. Available online at https://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html

[61] IARC (2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, World Health Organization, Lyon, France, p. 14. Available online at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

origin; diet composition; laboratory site, other animal husbandry conditions) may result in differences in response across animal carcinogenicity studies. Thus, consistency across animal studies is not required to establish a causal connection.

IARC concluded "[t]here is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate" based on findings from two studies in male mice. Specifically, IARC found "a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice" in a two-year diet study[62], and "a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma and carcinoma (combined)" in male CD-1 mice in a different two-year diet study[63], with IARC noting that these malignant kidney tumors are rare in this strain of mice. Thus, IARC found dose-related increases in tumor incidence in these studies and OEHHA agrees with this determination.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. No changes were made to the regulation based on this comment.

Comment 17 (Ramboll Environ, on behalf of The Scotts Company, LLC): "Conducting dose-response modeling with a limited dataset – such as the dataset used in the derivation of the NSRL for glyphosate, which provides the observation of incidence above zero only at the highest concentration – creates significant model uncertainty." They also state that "this type of dataset lacks the necessary information to inform the shape of the dose-response curve in the low concentration region, which is needed for extrapolation to concentrations relevant to the human population and thus to estimate the NSRL."

Response 17: The proposed NSRL for glyphosate is based on the results of the most sensitive scientific study deemed to be of sufficient quality from which an NSRL can be derived, pursuant to Section 25703. Use of the multistage cancer model is generally

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[62] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[63] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

accepted as the default approach to modeling lifetime cancer data as it is considered sufficiently flexible to fit most cancer bioassay data[64]. As stated in the ISOR for glyphosate[65], OEHHA determined that the study it used to derive the NSRL demonstrated a treatment-related increase in hemangiosarcomas, with a statistically significant positive trend. OEHHA disagrees with the commenter that modeling this data using the multistage cancer model "creates significant model uncertainty"; in fact, examination of the goodness-of-fit criteria[66,67] subsequent to fitting the model supports the appropriateness of the default approach. In particular, the global goodness-of-fit p-value is 0.9365, which is well above the cutoff of 0.05, the scaled residuals are all less than two in absolute value, and the plot shows that the multistage cancer model fits the data very well. The relatively low incidence of hemangiosarcoma in the high dose group (8%) effectively limits the possibilities the shape of the curve fit to the data can take. In fitting the multistage cancer model to this data, OEHHA followed the guidance in Section 25703, which is consistent with scientific practices in other OEHHA programs[68] and other scientific guidance, including US EPA's 2005 cancer risk assessment guidelines[69]. No changes were made to the proposed regulation based on this comment.

Comment 18 (Baum, Hedlund, Aristei & Goldman, P.C.): Section 25703(a)(1) requires that OEHHA consider the "degree to which dosing resembles the expected manner of human exposure" and "the route of exposure." The dietary ingestion of glyphosate as evaluated in the animal cancer bioassay considered by OEHHA does not resemble the expected manner of human exposure through application.

Response 18: The commenter has quoted only a portion of Section 25703(a)(1); OEHHA provides the full statement from the regulations for context and clarity:

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[64] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars.* Available from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[65] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[66] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars.* Available from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[67] US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf

[68] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[69] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

> "Animal bioassay studies for quantitative risk assessment shall meet generally accepted scientific principles, including the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence."

As can be seen in the full quotation of Section 25703(a)(1) above, "the degree to which dosing resembles the expected manner of human exposure" is one of *several* key considerations in determining whether or not an animal cancer bioassay is suitable for use in the development of an NSRL. OEHHA found the data used to derive the NSRL for glyphosate to be sufficient with respect to each of these considerations. With regard to the manner in which animals were dosed, diet is one of the expected routes of glyphosate exposure in humans and thus deriving the NSRL from study data in which test animals were administered glyphosate through the diet is consistent with the regulations. Animal bioassays employing dietary exposure are commonly used and routinely accepted for toxicity testing of pesticides.

Comment 19 (Dr. Thomas McDonald): OEHHA should make its own determination on the genotoxicity of glyphosate and not rely on IARC. He states that other authoritative bodies have concluded that glyphosate poses no genotoxicity risk in mammals, and that a Margin of Exposure (MOE) approach [to dose-response assessment] appears more appropriate.

Response 19: To the extent that the comment is directed toward the listing of glyphosate, it is not relevant to the determination of an NSRL for this chemical. OEHHA has reviewed the discussion of the mechanistic data for glyphosate provided in the IARC monograph and agrees with IARC's conclusion that "Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans."[70]

OEHHA notes that IARC[71] further elaborated on this evidence, stating:

- "There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals. One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation)

[70] IARC (2015) p. 78, full citation provided in footnote 3.
[71] IARC (2015) pp. 78-79, full citation provided in footnote 3.

were significantly greater after exposure than before exposure in the same individuals."

- "There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress."

OEHHA disagrees that a Margin of Exposure approach is more scientifically appropriate for derivation of the NSRL for glyphosate than the procedure used by OEHHA. Section 25703 sets forth a default approach, using a multistage model for deriving a cancer potency estimate, which is used "in the absence of principles or assumptions scientifically more appropriate"[72]. No information has been provided in support of another mechanism of action that would suggest a different approach to dose-response analysis.

In deriving the NSRL, OEHHA used the Benchmark Dose (BMD) method, as described both in OEHHA's guidance[73] and in the US EPA guidelines[74], applying a multistage mathematical model to describe the relationship between the risk of cancer and the dose. As part of the procedure OEHHA used for determining the cancer potency using the BMD method, a determination is made as to the proper type of extrapolation from the point of departure (typically the 95% lower confidence limit of the ED_{05} or ED_{10} for tumor induction) to low doses. OEHHA considered whether there was a more scientifically appropriate method for the NSRL derivation than linear extrapolation, but did not identify one, stating in the Initial Statement of Reasons:

> "Based on consideration of the available mechanistic information on glyphosate and the above conclusions reached by IARC[75], a multistage model is applied to derive a cancer potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach."[76]

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[72] Section 25703(a)
[73] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Available from: https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf
[74] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.
[75] IARC (2015). Full citation provided in footnote 3.
[76] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

No changes were made to the regulatory proposal based on this comment.

Comment 20 (Food Democracy Now, The Agricultural Council of California, The California Farm Bureau Federation, Monsanto, Ramboll Environ on behalf of The Scotts Company LLC, Anthony Samsel, Jessica Denning, and PT Rothschild): Suggest alternative values for the NSRL for glyphosate:

Anthony Samsel, Frank Menhams and others commented that a value of 0 µg/day should be used because there is no safe level of glyphosate.

PT Rothschild recommended setting an NSRL based on a concentration of 0.01 parts per trillion.

Jessica Denning recommended setting an NSRL based on a concentration of a concentration of 0.01 parts per trillion because at a part per trillion, breast cell proliferation occurs.

Food Democracy Now suggested 0.1 µg/day.

The Agricultural Council of California and the California Farm Bureau Federation request that the proposed NSRL [1,100 µg/day] be considered a minimum value and that no consideration be given to anything lower.

Monsanto states that glyphosate does not cause cancer, therefore, exposure at any level poses no significant risk of cancer to humans, therefore the NSRL should be infinite.

Ramboll Environ on behalf of The Scotts Company LLC, states that if OEHHA insists on setting an NSRL for glyphosate, it should be infinite.

Response 20: Section 25703 of the regulations states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[77]. Section 25703 further states that "risk analysis shall be based on the most sensitive study deemed to be of sufficient quality." No data that met these criteria were provided to support setting the NSRL at 0 or 0.1 µg/day, or setting an NSLR based on a concentration of 0.01 parts per trillion or 10 parts per quadrillion, nor were such data provided to support setting an infinite NSRL.

[77] Section 25703(a)(4)

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet met the criteria in 25703 precisely because this study led to the highest cancer potency and subsequently the lowest NSRL among studies deemed to be of comparable scientific validity as those which formed the scientific basis for the listing of glyphosate. As already noted, OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

No changes were made to the regulatory proposal based on this comment.

Comment 21 (The Environmental Working Group): OEHHA should set the limit at 10 µg/day which factors in a tenfold safety factor to account for the increased vulnerability of children, a one-in-a-million cancer risk standard used for carcinogens in drinking water, and rounding.

The commenter states that including a tenfold safety factor in the development of the NSRL for glyphosate is supported by OEHHA's 2009 report "*In Utero* and Early Life Susceptibility to Carcinogens", NRC's 1993 report "Pesticides in the Diets of Infants and Children", NRC's 2009 report "Science and Decisions" which advises public health agencies to include a factor of up to 25 to account for individual variation in susceptibility, and the 1996 Food Quality Protection Act which specifically required pesticide risk assessors to consider children's susceptibility to pesticides using a tenfold safety factor.

The commenter also states that OEHHA should use the one-in-a-million standard applied for carcinogens in drinking water for setting the NSRL for all exposures.

Response 21: The Food Quality Protection Act (FQPA), a federal law, is separate and distinct from Proposition 65, a California state law. Moreover, these two laws were established for different purposes and have different regulations and requirements. In particular, the FQPA relates to the setting of safety standards for pesticide residues in food, while Proposition 65 requires businesses to provide a warning when they cause an exposure to a listed chemical unless they can show the exposure does not exceed the safe harbor level, and prohibits the discharge of listed chemicals to sources of drinking water. Proposition 65 warnings are not required and the discharge prohibition does not apply when exposures are at or below the safe harbor level.

The NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in

question"[78]. Thus, OEHHA cannot use a one-in-a-million level of risk in setting the NSRL. Similarly, OEHHA cannot apply a tenfold safety factor to the NSRL. The NSRL for glyphosate was derived according to the requirements set forth in Section 25703.

NSRLs do not conflict with permissible levels set by the federal government or with the one-in-a-million cancer risk standard for carcinogens in drinking water. These other laws have no bearing on Proposition 65, and it has no bearing on them. No changes to the regulatory proposal were made based on this comment.

Comment 22 (Food Democracy Now!, Joanie Blaxter): OEHHA should wait to consider a high NSRL for glyphosate until the studies showing carcinogenic effects in human populations can be replicated and extended. Joanie Blaxter commented that the testing model should be replaced with a more real life model of the effects of sub-acute low-level exposure over long periods of time in combination with exposure to other potentially activating chemicals and heavy metals.

Response 22: As stated in the response to Comment 1, glyphosate was listed pursuant to the Labor Code listing mechanism[79] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of "sufficient evidence of carcinogenicity in experimental animals" and "limited evidence" in humans[80,81]. Section 25703 of the regulations states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[82]. Given that the listing of glyphosate is based on sufficient evidence in animals, basing the potency estimate for the NSRL on animal studies is both appropriate and consistent with Section 25703. It is not appropriate for OEHHA to wait for additional studies to be conducted in humans, or otherwise delay the adoption of the NSRL for glyphosate, which is intended to aid businesses in complying with Proposition 65. Should additional scientific studies become available in the future that meet the criteria set out in Section 25703, OEHHA can consider revising the NSRL for glyphosate at that time. No changes were made to the regulatory proposal based on this comment.

Comment 23 (Comments from Food Democracy Now): "A two year study on rats published in 2015 found that just 0.05 ppb changed the function of more than 4000 genes. It would behoove the commission to pay attention to any and all studies which

[78] Section 24703.
[79] Section 25249.8(a) of the Act
[80] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[81] IARC (2015). Full citation provided in footnote 3.
[82] Section 25703(a)(4)

suggest adverse human health effects at such miniscule levels. The study found steatohepatosis which predisposes to liver cancer at a glyphosate equivalent dose of only 4 nanograms per kg per day. The amount of glyphosate ingested by these rats is approximately 4000 times lower than what is typically ingested based on levels found in urine. This is the only study of its type providing a direct causative link between an environmentally relevant dose of Roundup and a serious disease."

Response 23: The commenter appears to be referring to a 2015 publication by Mesnage *et al.*[83], that analyzed differences in gene expression, not gene function, in the liver and kidney of female rats administered a glyphosate-based herbicide in drinking water for two years, as compared with controls receiving "plain water". Changes in gene expression levels were observed for more than 4000 genes in the liver and kidney of treated animals, as compared with controls. Treatment-related tumors were not reported in this study. This study does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL. No changes were made to the regulatory proposal based on this comment.

Comment 24 (A number of commenters, including Meghan Lawler): Raised concerns about exposure to glyphosate, whether through food, consumer products, the environment, or during application as a pesticide. Some state that the proposed NSRL does not reflect real-world exposure scenarios or expected exposure concentrations. Some state that it is unclear how the increased exposure of agricultural workers will be factored in, when setting an NSRL. Some have reported various levels that a typical adult is exposed to on a daily basis. Some state that there is no way to establish or enforce a safe level because it is impossible to quantify cumulative exposure. Meghan Lawler commented that no comprehensive, long term, independent study has been done that shows real life exposure levels for glyphosate.

Response 24: Following the guidance set forth in Section 25703, NSRLs are based on cancer dose-response assessments, which are conducted using tumor incidence data from the most sensitive scientific studies deemed to be of sufficient quality. Cancer dose-response assessments are performed to estimate a carcinogen's cancer potency, and the NSRL is derived based on the cancer potency estimate. Specifically, the NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question"[84]. Thus, the NSRL is a level of exposure or intake, expressed in units of µg/day that is associated with a risk of cancer of one-in-100,000.

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[83] Mesnage R, Arno M, Costanzo M, Malatesta M, Seralini G-E, Antoniou MN (2015). Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environmental Health* 14:70 DOI 10.1186/s12940-015-0056-1.

[84] Section 24703.

Exposure information (*e.g.*, exposure routes, exposure levels) is not used in dose-response assessment. Rather, estimates of exposure may be used *together* with estimates of cancer potency to predict cancer risk within a population.

As noted in response to comment 1, the estimate of cancer potency for glyphosate is equally valid for estimating risks to agricultural workers and to other exposed individuals, and the NSRL for glyphosate is not limited to a specific route of exposure[85,86].

Many conventional regulatory standards are developed using the kind of real-world exposure information cited by the commenters. Those standards identify legally mandated, health-protective levels of exposures to chemicals that can be feasibly achieved by manufacturers and employers. The NSRL is not a conventional regulatory standard, as it is based strictly on the scientific criteria cited above. It is intended to guide businesses in determining whether a warning is necessary or whether discharges of a chemical into drinking water sources are prohibited. A Proposition 65 warning enables Californians to make informed choices about their exposures to listed chemicals.

Comment 25 (Several commenters): The proposed level is too high, and one commenter stated that, in comparison, the NSRL for TCDD is much lower.

Response 25: The comment compares the proposed NSRL for glyphosate, 1100 µg/day, to the NSRL for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is 0.000005 µg/day. It has long been recognized that carcinogens vary in strength, or potency, with some being extremely potent, and others much less potent[87]. Indeed, the cancer potencies of carcinogens vary by several orders of magnitude[88]. NSRLs, which are derived from cancer potency estimates, can similarly vary by orders of magnitude, as can be seen when comparing the NSRL for glyphosate to that for TCDD. Thus, the fact that the NSRL for glyphosate is much higher than the NSRL for TCDD is not an indication that the glyphosate NSRL is too high, or otherwise inappropriate.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study

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[85] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[86] Section 25703(a)(4)

[87] Gold, L. S., et al. (1984) A carcinogenic potency database of the standardized results of animal bioassays. *Environ Health Perspect* **58**: 9-319.

[88] *Ibid.*

conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet met the criteria in 25703 precisely because this study led to the highest cancer potency and subsequently the lowest NSRL among studies deemed to be of comparable scientific validity as those which formed the scientific basis for the listing of glyphosate. As already noted, OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related. No changes were made based on this comment.

Comment 26 (Laura Hayes, Pesticide Free Zone and Tamsin Lisa Kelly, JD, MD): The proposed level is a random rate that cannot be accurately monitored or enforced. Pesticide Free Zone asked how OEHHA would determine the amount that humans are exposed to on a daily basis. Tamsin Lisa Kelly, JD, MD, stated that if use is allowed, testing of food and water supplies must be required regularly to assure exposure is limited.

Response 26: OEHHA disagrees with the statement that the proposed NSRL for glyphosate is a random rate. As described in more detail in Response 19 OEHHA followed standard cancer dose-response assessment practice in deriving an NSRL of 1100 µg/day for glyphosate, which is based on the most sensitive study of sufficient quality. OEHHA's approach is consistent with Section 25703, scientific practices in other OEHHA programs[89] and other scientific guidance, including US EPA's 2005 cancer risk assessment guidelines[90].

OEHHA has no authority under Proposition 65 to monitor exposures to listed chemicals. Businesses are responsible for determining if they are causing exposures to listed chemicals at levels that require warnings. The purpose of the NSRL is to assist businesses in making these determinations. Similarly, OEHHA has no authority under Proposition 65 to require testing of food and water supplies. No changes were made to the regulatory proposal based on this comment.

Comment 27 (A Voice for Choice, Organic Sacramento, and several others): The NSRL does not account for differences in vulnerability due to size, age, stage of development, health status, or socioeconomic status.

Response 27: As specified in Section 25703, the "risk analysis shall be based on the most sensitive study deemed to be of sufficient quality", and "the risk level which represents no significant risk shall be one which is calculated to result in one excess

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[89] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[90] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

case of cancer in an exposed population of 100,000, **assuming lifetime exposure at the level in question**". (Emphasis added)

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. The calculation assumes lifetime exposure at the level in question to an average person in the general population. No changes were made to the regulation based on this comment.

Comment 28 (A number of commenters): Urge OEHHA to ban glyphosate, that it be declared a "restricted use" chemical, that it not be available to the public, or that OEHHA should ensure labeling of all products, businesses, and public spaces containing any amount of glyphosate. Bob Sanders commented that instead of considering an NSRL, OEHHA should be discussing glyphosate as "not safe for human consumption" (NSFHC) and including 10 mile safety zones to protect children and families.

Response 28: Proposition 65 does not give OEHHA authority to remove products or chemicals from the market or to restrict their use. While OEHHA has regulatory authority to broadly identify acceptable methods and content for Proposition 65 warnings, OEHHA does not have the authority to directly regulate product labeling as suggested by the commenters. Similarly, Proposition 65 does not give OEHHA the authority to categorize glyphosate as not safe for human consumption or to impose safety zones as suggested by the commenter. These comments are outside the scope of the current rulemaking and no changes were made based on this comment.

Comment 29 (Larry Wartels, Susan[91] and others): OEHHA should use the precautionary principle in developing the NSRL for glyphosate. OEHHA should only allow use of the lowest effective levels of glyphosate so that plants do not become glyphosate resistant.

Response 29: In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 of the regulations, which states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[92]. Glyphosate was listed pursuant to the Labor Code listing mechanism[93] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of sufficient evidence of

[91] The commenter did not provide a last name.
[92] Section 25703(a)(4)
[93] Section 25249.8(a) of the Act

carcinogenicity in experimental animals[94,95]. OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC[96], and determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met the criterion in Section 25703 as the most sensitive study of sufficient quality. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related. OEHHA then performed a standard dose-response assessment using the data from this study to derive the NSRL for glyphosate. The resistance of plants to glyphosate is not relevant for purposes of deriving an NSRL. No changes were made based on this comment.

Comment 30 (One commenter (anonymous)): Extrapolating cancer risk to humans from hemangiosarcomas, which are very rare in humans, seems misleading and to use this to determine the NSRL seems unscientific.

Response 30: The premise underlying this comment is incorrect. It is a generally accepted principle that the ability of a chemical to cause cancer in animals is predictive that the chemical also poses a cancer hazard in humans[97]. However, it is not assumed that the same tumor type observed in animals will be observed in humans[98]. Similarly, the fact that cancer potency is estimated based on animal tumor data for a particular tumor type does not imply that the cancer potency applies specifically to that same tumor type in humans. The human cancer potency estimate is a measure of the carcinogenic hazard posed by a particular carcinogen, and can be used to estimate the risk of cancer (at all sites that may be affected by this carcinogen) associated with a specific level of exposure in humans. No changes were made in response to this comment.

Comment 31 (Baum, Hedlund, Aristei & Goldman, P.C., Meredith Newton, Timothy Litzenburg and others): Raised concerns over OEHHA meeting with representatives from Monsanto in October 2015. The commenters state that OEHHA should be presented with an impartial and comprehensive scope of data in determining the NSRL and that industry meetings with regulators should be open to public scrutiny. Timothy

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[94] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. Available from: https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[95] IARC (2015). Full citation provided in footnote 3.
[96] IARC (2015). Full citation provided in footnote 3.
[97] IARC (2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization, International Agency for Research on Cancer, Lyon, France, 2006. Available from: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)
[98] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

Litzenburg] requested that OEHHA schedule a meeting with stakeholders before making a decision on the safe harbor threshold.

Response 31: This comment is not directed towards the rulemaking. In compliance with the Administrative Procedure Act (APA), OEHHA published a Notice of Proposed Rulemaking, thereby opening a 45-day public comment period, and held a public hearing where all interested parties were allowed to provide their input regarding the proposed rulemaking. OEHHA provided the public with the opportunity to provide written comments during the comment period. OEHHA is publicly responding to all the oral and written comments received during the rulemaking in this Final Statement of Reasons. Nothing in the APA prohibits OEHHA from meeting with stakeholders to hear all viewpoints on an issue. The October 2015 meeting occurred before glyphosate was added to the Proposition 65 list of chemicals and before the current rulemaking proposal. OEHHA also met with many of the commenters, including representatives of Baum, Hedlund, Aristei & Goldman, P.C. and Timothy Litzenburg and others in August 2017 to understand their position concerning the NSRL. No changes were made to the proposed regulation based of this comment.

Comment 32 (Zen Honeycutt): Section 25703 requires OEHHA to consider all available studies showing harm. Provided many references for OEHHA's consideration, many of which were not included in IARC's review (Table 2.)

Response 32: Section 25703 does not mandate a review of all available studies showing harm. Rather Section 25703 requires that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and the NSRL must be based on the results of the most sensitive scientific study deemed to be of sufficient quality.

Of the 72 published scientific articles listed in the comments from Zen Honeycutt, 54 were not cited in the IARC Monograph[99] that OEHHA relied on in developing the NSRL for glyphosate. These 54 publications are listed in Table 2. OEHHA reviewed each of these publications in the context of the guidance set forth in Section 25703, i.e., "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[100] and determined that none of the studies provide data that would affect the cancer dose-response analysis (See Table 2). No changes were made to the regulatory proposal based on this comment.

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[99] IARC (2015). Full citation provided in footnote 3.
[100] Section 25703(a)(4)

Table 2. Studies related to glyphosate that were identified by Zen Honeycutt and not considered by IARC

Reference	Comments
Arbuckle TE, Lin Z, Mery LS (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect* **109**(8):851-7.	This human epidemiological study investigated the effects of glyphosate exposure on spontaneous abortion. This reproductive toxicity study is not relevant to cancer dose-response analysis.
Astiz M, Alaniz MJT de, Marra CA (2009). The impact of simultaneous intoxication with agrochemicals on the antioxidant defense system in rat. *Pesticide Biochemistry and Physiology* **94**:93-99.	This study in rats examined the effects of glyphosate on oxidative stress, and hormone levels. This mechanistic study does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Barbosa ER, Leiros da Costa MD, Bacheschi LA, Scaff M, Leite CC (2001). Parkinsonism after glycine-derivate exposure. *Mov Disord* **16**(3):565-8.	This is a case report of an incidence of Parkinson's disease following exposure to glyphosate, and is not relevant to cancer dose-response analysis.
Bellé R, Le Bouffant R, Morales J, Cosson B, Cormier P, Mulner-Lorillon O (2007). Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development. *J Soc Biol* **201**(3):317-27. [Article in French]	This study examined the effects of glyphosate on sea urchin development. This toxicity study may provide data on possible mechanisms of action, but it does not provide data that can be used in the cancer dose-response analysis.
Benedetti AL, Vituri Cde L, Trentin AG, Domingues MA, Alvarez-Silva M (2004). The effects of sub-chronic exposure of Wistar rats to the herbicide Glyphosate-Biocarb. *Toxicol Lett* **153**(2):227-32.	This study examined the effects of Glyphosate-Biocarb® on the livers of Wistar rats following 75 days of exposure. This subchronic toxicity study does not provide data that can be used in the cancer dose-response analysis.
Benedetti D, Nunes E, Sarmento M, Porto C, Dos Santos CE, Dias JF, da Silva J (2013). Genetic damage in soybean workers exposed to pesticides: evaluation with the comet	This study in farm workers assessed the effects of exposure to complex mixtures of pesticides, including glyphosate, on DNA. The authors reported that DNA damage and genomic hypermethylation of DNA were significantly increased in individuals exposed

and buccal micronucleus cytome assays. *Mutat Res* **752**(1-2):28-33.	to pesticide mixtures, but it does not provide data that can be used in the cancer dose-response analysis.
Beuret CJ, Zirulnik F, Giménez MS (2005). Effect of the herbicide glyphosate on liver lipoperoxidation in pregnant rats and their fetuses. *Reprod Toxicol* **19**(4):501-4.	This study investigated the effects of glyphosate on pregnant female Wistar rats and their fetuses. This reproductive toxicity study provides no data that can be used in the cancer dose-response analysis.
Cox C (2004). Herbicide factsheet: glyphosate. *Journal of Pesticide Reform* **24**(4):10-15.	This factsheet is a short review and does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
da Costa Mdo D, Gonçalves LR, Barbosa ER, Bacheschi LA (2003). Neuroimaging abnormalities in parkinsonism: study of five cases. *Arq Neuropsiquiatr* **61**(2B):381-6. [Article in Portuguese]	This study reports neuroimaging results in five patients with Parkinson's disease, one of whom was exposed to glyphosate. This study is not relevant to cancer dose-response analysis.
Dallegrave E, Mantese FD, Coelho RS, Pereira JD, Dalsenter PR, Langeloh A (2003). The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats. *Toxicol Lett* **142**(1-2):45-52.	This study examined the teratogenicity of glyphosate-Roundup® to Wistar rats. This developmental toxicity study provides no data relevant to cancer dose-response analysis.
Dallegrave E, Mantese FD, Oliveira RT, Andrade AJ, Dalsenter PR, Langeloh A (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. *Arch Toxicol* **81**(9):665-73.	This study investigated the reproductive effects of glyphosate-Roundup® on male and female offspring of Wistar rats exposed during pregnancy and lactation. This reproductive toxicity study provides no data relevant to cancer dose-response analysis.
Daruich J, Zirulnik F, Gimenez MS (2001). Effect of the herbicide glyphosate on enzymatic activity in pregnant rats and their fetuses. *Environ Res* **85**(3):226-31.	This study investigated the effects of glyphosate exposure to pregnant Wistar rats on enzymes in the dams and their fetuses. This reproductive toxicity study provides no data relevant to cancer dose-response analysis.
de Liz Oliveira Cavalli VL, Cattani D, Heinz Rieg CE, Pierozan P, Zanatta L, Benedetti Parisotto E, Wilhelm	This study investigated the effects of glyphosate on male rat Sertoli cells and testis

Filho D, Mena Barreto Silva FR, Pessoa-Pureur R, Zamoner A (2013). Roundup disrupts male reproductive functions by triggering calcium-mediated cell death in rat testis and Sertoli cells. *Free Radic Biol Med* **65**:335-46.	*in vitro*. This *in vitro* toxicity study provides no data to cancer dose-response analysis.
de Souza JS, Kizys MM, da Conceição RR, Glebocki G, Romano RM, Ortiga-Carvalho TM, Giannocco G, da Silva ID, Dias da Silva MR, Romano MA, Chiamolera MI (2017). Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats. *Toxicology* **377**:25-37.	This study investigated the effects of a glyphosate-based herbicide on the hypothalamic-pituitary-thyroid axis of male rats following *in utero* exposure. The authors reported that exposure affected thyroid hormone homeostasis. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Geng D et al. (2000). Study of Herbicide Roundup impact on yellow eel mutagenic. *Journal of Xuzhou Normal University* (Natural Science Edition) **2**. [Article in Chinese] Available from http://www.cnki.com.cn/ Article/ CJFDTotal-XZSX200002018.htm	This study investigated the genotoxicity of glyphosate in the erythrocytes of *Monopterus albus* (Asian swamp eel) *in vivo*. It suggests that glyphosate induces chromosomal aberrations. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Hokanson R, Fudge R, Chowdhary R, Busbee D (2007). Alteration of estrogen-regulated gene expression in human cells induced by the agricultural and horticultural herbicide glyphosate. *Hum Exp Toxicol* **26**:747-52.	This *in vitro* study investigated the effects of glyphosate on human MCF-7 cells and found altered gene expression. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Huang C, Li B, Xu K, Liu D, Hu J, Yang Y, Nie H, Fan L, Zhu W (2017). Decline in semen quality among 30,636 young Chinese men from 2001 to 2015. Fertil Steril **107**(1):83-88.	This study provides no information or data that is specific to glyphosate.
Jayawardena UA, Rajakaruna RS, Navaratne AN, Amerasinghe PH	This toxicity study of glyphosate and other pesticides observed malformations in exposed

(2010). Toxicity of agrochemicals to common hourglass tree frog (*Polypedates cruciger*) in acute and chronic exposure. *International Journal of Agriculture and Biology*, 12, 641-648.	tree frogs. This study provides no data relevant to cancer dose-response analysis.
Kamel F, Tanner C, Umbach D, Hoppin J, Alavanja M, Blair A, Comyns K, Goldman S, Korell M, Langston J, Ross G, Sandler D (2007). Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. *Am J Epidemiol* **165**(4):364-74.	This study on Parkinson's disease is not relevant to cancer dose response-analysis.
Kang J et al. (2008). Study of glyphosate effect causing mutagenic on rats. Carcinogenesis, Teratogenesis & Mutagenesis **3**. [Article in Chinese] Available from http://www.cnki.com.cn/ Article/ CJFDTotal-ABJB200803018.htm	The hyperlink provided by the commenter leads to an article by Kang et al. (2008), named "Study on mutagenesis induced by glyphosate in mice". The full text also indicates that this study was in mice, but not rats. Other than the title, the rest of the citation is correct. This study reports that glyphosate induced micronucleus formation in bone marrow polychromatic erythrocytes of Kunming mice, increased sperm aberrations, and decreased sperm count. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Kruger M, Schledorn P, Schrodl W, Hoppe HW, Lutz W, Shehata AA (2014). Detection of Glyphosate Residues in Animals and Humans. *J Environ Anal Toxicol* **4**(2):210.	This study measured glyphosate residues in animals and humans using ELISA and gas chromatography-mass spectroscopy. Glyphosate residues were detected in the kidney, liver, lung, spleen, muscles, and intestine in dairy cows (minimum = 1.36 µg/g; maximum of 108 µg/mg). Glyphosate residues were detected in the urine of dairy cows (minimum = 0 µg/ml; maximum = 164

	µg/ml), rabbits (minimum = 2.37 µg/ml; maximum = 70 µg/ml) and humans (minimum = 0.1 µg/ml; maximum = 71.3 µg/ml). Significantly higher urinary glyphosate residues were reported in chronically ill humans than in healthy individuals. This study provides no data relevant to cancer dose response analysis.
Lajmanovich RC, Sandoval MT, Peltzer PM (2003). Induction of mortality and malformation in Scinax nasicus tadpoles exposed to glyphosate formulations. *Bull Env Contam Toxicol* **70**:612–618.	This study investigated the effects of glyphosate on tadpoles exposed for 96 hours. This acute toxicity study in amphibians provides no data relevant to cancer dose-response analysis.
Li Q, et al. (2010). Acute toxicity of eight types of pesticides to sea urchin embryos during different phases of development. *Asian Journal of Ecotoxicology*. [Article in Chinese] Available from http://d.wanfangdata.com.cn/Periodical_cyyhj 201002014.aspx	This study investigated the acute toxicity of glyphosate on the development of sea urchin embryos. This study provides no data relevant to cancer dose-response analysis.
Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, Di Berardino D, Ursini MV (1998). Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to glyphosate, vinclozolin, atrazine, and DPXE9636. *Environ Mol Mutagen* **32**(1):39-46.	This *in vitro* study in human peripheral lymphocytes reported that glyphosate exposure increased chromosomal aberrations, sister chromatid exchanges, and a change in the redox state of the cell. This study contributes to the data on possible mechanisms of action, but it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Marc J, Mulner-Lorillon O, Boulben S, Hureau D, Durand G, Bellé R (2002). Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. *Chem Res Toxicol* **15**(3):326-31.	This study investigated the effects of Roundup® and glyphosate on cell cycle regulation in sea urchin embryos. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.

Marc J, Bellé R, Morales J, Cormier P, Mulner-Lorillon O (2004a). Formulated glyphosate activates the DNA-response checkpoint of the cell cycle leading to the prevention of G2/M transition. *Toxicol Sci* **82**(2):436-42.	This *in vitro* study investigated the effects of glyphosate on the cell cycle of sea urchins. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Marc J, Mulner-Lorillon O, Bellé R (2004b). Glyphosate-based pesticides affect cell cycle regulation. *Biol Cell* **96**(3):245-9.	This paper investigated the effects of several glyphosate-based pesticides on cell cycle regulation in sea urchins. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Marc J, Le Breton M, Cormier P, Morales J, Bellé R, Mulner-Lorillon O (2005). A glyphosate-based pesticide impinges on transcription. Toxicol Appl Pharmacol **203**(1):1-8.	This study investigated the effects of glyphosate on sea urchin development and found effects on transcription in early development. This study does not provide data that can be used in the cancer dose-response analysis.
McComb BC, Curtis L, Chambers CL, Newton M, Bentson K (2008). Acute toxic hazard evaluations of glyphosate herbicide on terrestrial vertebrates of the Oregon Coast Range. *Environ Sci Pollut Res Int* **15**(3):266-72.	This study evaluated the effects of acute exposure to glyphosate on white lab mice and 9 wild vertebrate species from the Oregon coast (deer mouse, chipmunk, shrew, vole, newt, frog, and three types of salamanders). This acute toxicity study does not provide data that can be used in the cancer dose-response analysis.
Mesnage R, Clair E, Spiroux de Vendômois J, Séralini GE (2010). Two cases of birth defects overlapping Stratton-Parker syndrome after multiple pesticide exposure. *Occup Environ Med* **67**(5):359.	This is a report of two instances of congenital malformations in children whose parents had been exposed to multiple pesticides, including glyphosate. These case reports are not relevant to cancer dose-response analysis.
Mesnage R, Renney G, Seralini GE, Ward M (2017) Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide. *Sci Rep* **7**:39328.	This study used metabolome and proteome analyses of rat liver tissue to investigate the effects of low-dose exposure of rats to a glyphosate-based herbicide. The authors concluded that the metabolome and proteome changes observed were indicative of non-alcoholic fatty liver disease. This study does

	not provide data that can be used in the cancer dose-response analysis.
Nan X (2001). Impact of glyphosate herbicide on carp peripheral blood erythrocyte micronucleus and nuclear anomalies, *Journal of Anhui Normal University* (Natural Science Edition) **24**(4): 329-331. [Article in Chinese] Available from http://www.cqvip.com/qk/97138X/200006/ 4887295.html	The hyperlink provided by the commenter leads to a study by Nan et al. (2000), titled "Effects of Herbicide (Glyphosate) on Micronuclei and Nuclear Anomalies in Erythrocyte of Bufo bufo Gargarizans". It was conducted in Asiatic toads, not carp as the title provided by the commenter states. This study found that glyphosate increased the frequency of micronuclei and nuclear abnormalities in the erythrocytes of Asiatic toads after oral treatment. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Nan X (2002). Study of impact of glyphosate herbicide on carp blood cells and hemoglobin. *Gansu Science* **2**. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-GSKX200204015.htm	This study investigated the toxicity of glyphosate on carp (*Carassius auratus*) by measuring hemoglobin levels and erythrocyte and leucocyte counts. This study provides no data relevant to cancer dose-response analysis.
Nan X et al. (2003). Impact of glyphosate herbicide on loach white blood cells. *Journal of Wenzhou Normal University* (Natural Science Edition) **24**(2): 72-74. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WZSF200302019.htm	The hyperlink provided by the commenter leads to an article by Nan et al. (2003), titled "Effect of Mi[s]gurnus Anguillicaudatus induced by glyphosate". Other than the title, the rest of the citation is correct. This study investigated the effect of glyphosate on lymphocyte and granulocyte counts in the peripheral blood of *Misgurnus Anguillicaudatus* (pond loach, a fresh water fish). This study provides no data relevant to cancer dose-response analysis.

Negga R, Stuart JA, Machen ML, Salva J, Lizek AJ, Richardson SJ, Osborne AS, Mirallas O, McVey KA, Fitsanakis VA (2012). Exposure to glyphosate- and/or Mn/Zn-ethylene-bis-dithiocarbamate-containing pesticides leads to degeneration of γ-aminobutyric acid and dopamine neurons in *Caenorhabditis elegans*. *Neurotox Res* **21**(3):281-90.	This study on the effect of glyphosate on neurons in the roundworm *C. elegans* provides no data relevant to cancer dose response-analysis.
Oliveira AG, Telles LF, Hess RA, Mahecha GA, Oliveira CA (2007). Effects of the herbicide Roundup on the epididymal region of drakes Anas platyrhynchos. *Reprod Toxicol* **23**(2):182-91.	This study investigated the effects of Roundup® on the epididymis and testes of adult male ducks exposed for 15 days. This male reproductive toxicity study provides no data relevant to cancer dose-response analysis.
Perkins PJ, Boermans HJ, Stephenson GR (2000). Toxicity of glyphosate and triclopyr using the frog embryo teratogenesis assay—*Xenopus*. *Environmental Toxicology and Chemistry* **19**: 940–945.	The effects of glyphosate were studied on the embryonic development of *Xenopus laevis.* This developmental toxicity study is not relevant to cancer dose-response analysis.
Relyea RA (2012). New effects of Roundup on amphibians: predators reduce herbicide mortality; herbicides induce antipredator morphology. *Ecol Appl* **22**(2):634-47.	This study examined the effects of Roundup on the response of amphibians to predators. This behavioral study is not relevant to cancer dose-response analysis.
Romano RM, Romano MA, Bernardi MM, Furtado PV, Oliveira CA (2010). Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. *Arch Toxicol* **84**(4):309-17.	This paper reports the effects of glyphosate on testicular development in male rats exposed on postnatal days 23 to 53. This study does not provide data that can be used in the cancer dose-response analysis.
Roy NM, Ochs J, Zambrzycka E, Anderson A (2016). Glyphosate induces cardiovascular toxicity in *Danio rerio*. *Environmental Toxicology and Pharmacology*	This study investigated the effects of glyphosate on heart development in zerbrafish. This developmental toxicity study is not relevant to cancer dose-response analysis.

46:292–300.	
Savitz DA, Arbuckle T, Kaczor D, Curis KM (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol* **146**(12):1025-35.	This human epidemiology study assessed pesticide exposure, including exposure to glyphosate, on male reproductive outcomes. This male reproductive toxicity study is not relevant to cancer dose-response analysis.
Soso AB, Barcellos LJ, Ranzani-Paiva MJ, Kreutz LC, Quevedo RM, Anziliero D, Lima M, Silva LB, Ritter F, Bedin AC, Finco JA (2007). Chronic exposure to sub-lethal concentration of a glyphosate-based herbicide alters hormone profiles and affects reproduction of female Jundiá (Rhamdia quelen). *Environ Toxicol Pharmacol* **23**:308–313.	This study examined the effects of glyphosate on the Jundia fish and found effects on reproductive status. This fish reproductive toxicity study does not provide data that can be used in the cancer dose-response analysis.
Soto AM, Sonnenschein C (2010). Environmental causes of cancer: endocrine disruptors as carcinogens. *Nat Rev Endocrinol* **6**(7):363-70.	This study provides no data specific to glyphosate.
Sparling DW, Matson C, Bickham J, Doelling-Brown P (2006). Toxicity of glyphosate as Glypro and LI700 to red-eared slider (trachemys scripta elegans) embryos and early hatchlings. *Environ Toxicol Chem* **25**(10):2768-74.	This study examined the effects of glyphosate on the development of turtle eggs. This developmental toxicity study in turtles is not relevant to cancer dose-response analysis.
Swanson NL, Leu A, Abrahamson J, Wallet B (2014). Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. *Journal of Organic Systems* **9**(2).	This descriptive study conducted correlation analyses based on time trends in genetically engineered crop data, glyphosate application data, and disease rates in the US. A significant correlation was reported between glyphosate application rates and incidence of thyroid, liver, bladder, pancreas, and kidney cancer, and myeloid leukemia. Incidences of these cancers were also correlated with percentages of genetically engineered corn and soy planted in the US.

	This descriptive study provides correlations between glyphosate usage and disease rates. However, a descriptive study does not provide evidence of causation. Additionally, there is a latency period between exposure to a carcinogen and development of cancer. In this study, however, there was often a temporal overlap between increases in glyphosate use and increases in cancer incidence (e.g., no evidence of latency between exposure and cancer). In some cases, cancer incidences increased before glyphosate use did. Descriptive studies such as this do not provide data that can be used in cancer dose-response analysis.
van der Mark M, Brouwer M, Kromhout H, Nijssen P, Huss A, Vermeulen R (2012). Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. *Environ Health Perspect* **120**(3):340-7.	This paper conducted a systematic review and meta-analysis of pesticide use (including glyphosate) and Parkinson's disease. This study on Parkinson's disease is not relevant to cancer dose response-analysis.
Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. *Endocr Rev*. 2012;33(3):378-455.	This study provides no data specific to glyphosate.
Wang G, Fan XN, Tan YY, Cheng Q, Chen SD (2011). Parkinsonism after chronic occupational exposure to glyphosate. *Parkinsonism Relat Disord* **17**(6):486-7.	This study on Parkinson's disease is not relevant to cancer dose-response analysis.
Wu H (1996). Glyphosate impact on rat cytochrome P450 2 B1 and P450 2 c11 gene expression. *Health*	The hyperlink provided by the commenter leads to an article by Wu and Prough (1996), titled "CYP450 2B1 and 2C11 expression in

Toxicology Journal, **10**(4): 231-234 [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WSDL604.004.htm	rat by glyphosate". Other than the different title, the rest of the citation is correct. This study examined liver microsomal enzyme activity as well as expression levels of CYP450 2B1 and 2C11 mRNA in rats after glyphosate treatment by oral gavage. This study does not provide data that can be used in the cancer dose-response analysis.
Yousef MI, Salem MH, Ibrahim HZ, Helmi S, Seehy MA, Bertheussen K (1995). Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits. *J Environ Sci Health B* **30**(4):513-34.	This study investigated the effects of glyphosate on body weight and semen in male New Zealand white rabbits exposed for six weeks. This male reproductive toxicity study is not relevant to cancer dose-response analysis.
Yu H et al. (2012). Progress in study of glyphosate toxicity **6**. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTOTAL-BANG201206050.htm and http://www.doc88.com/p-666125982792.html	This is a review of literature on the toxicity of glyphosate. This review did not identify any studies that would affect the cancer dose-response analysis.
Zeng M, Huang T et al. (2014). Glyphosate toxicity to mice GC-1 sperm cells and the interference effect of N-acetyl cysteine, *Ecological Toxicology Bulletin* **1.** [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-STDL201401031.htm	The hyperlink provided by the commenter leads to an article by Zeng et al. (2014), titled "Cytotoxicity of Glyphosate to GC-1 Mice Spermatogonium and Antagonistic Effects of N-acetylcysteine". Other than the title, the rest of the citation is correct. This study examined the cytotoxicity of glyphosate on GC-1 (mouse spermatogonia) cells. The study found that glyphosate induced DNA damage as shown by the Comet assay, and suggests that glyphosate may increase reactive oxygen species production in GC-1 cells. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Zhao W et al. (2011). Study of oxidative damage of the body	This study examined oxidative damage induced by glyphosate in Kunming mice.

caused by glyphosate. *Toxiology Journal* **25**(5):364-366 [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WSDL201105013.htm	Oxidative damage was measured as levels of total antioxidant capacity (TAC) and malondialdehyde (MDA) in serum and several tissues, and as serum levels of advanced oxidation products. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Zhao W, Yu H, Zhang J, Shu L (2013). Effects of glyphosate on apoptosis and expressions of androgen-binding protein and vimentin mRNA in mouse Sertoli cells. *Journal of Southern Medical University* **33**(11):1709-1713. [Article in Chinese]	This *in vitro* study investigated the effects of glyphosate on cultured mouse Sertoli cells. This male reproductive toxicity study does not provide data that can be used in the cancer dose-response analysis.

Comment 33: Teri Persico, Sandy DeSimone, William Brooks, Dr. Stephanie Seneff, and a number of other commenters provided lists of references for OEHHA's consideration.

Response 33: Of the published scientific articles listed in these comments, OEHHA carefully reviewed each of the cited documents in the context of the guidance set forth in Section 25703, in the same manner as was done in response to comment 32 above. Specifically the regulations states that "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer".[101] OEHHA determined that none of the cited studies provide data that would affect the cancer dose-response analysis[102]. No changes were made to the regulatory proposal based on these comments.

Comment 34 (Baum, Hedlund, Aristei and Goldman, P.C.): "Additional documents pertinent to the Safe Harbor NSRL and Roundup/glyphosate carcinogenicity are presently still under seal and it is strongly recommended that OEHHA obtain access to

[101] Section 25703(a)(4)
[102] In fact, most of the articles were unrelated to carcinogenicity and instead focused on topics such as ecotoxicity, environmental fate and transport, analytical methods, mechanisms unrelated to carcinogenicity, and more.

such documents before OEHHA takes the potentially precarious step of issuing an NSRL of 1100 micrograms."

Response 34: OEHHA used publicly available scientific studies to calculate the NSRL. There is no legal basis for OEHHA to ask a court in a third party matter to provide it with sealed documents. In the event these materials become publicly available in the future and they are relevant to the calculation of the NSRL, OEHHA can reconsider the NSRL at that time. No changes were made to the regulatory proposal based on this comment.

Comment 35: Carcinogen Identification Committee members Dr. Jason Bush, Dr. Luoping Zhang, and Dr. Shanaz Dairkee had no objections to the proposed NSRL. Colton Bond commented that the NSRL is a reasonably conservative benchmark. Chris Portier supported use of the multistage model and the extrapolation plan for the evaluation of glyphosate carcinogenicity. Anne Surdzial recommended that OEHHA adopt the NSRL as is, which is supported by science.

Response 35: No response is required. No changes were made to the regulatory proposal based on this comment.

Comment 36 (Linda Causey): Request determination on the economic cost to finding glyphosate in California wines.

Response 36: This comment is not related to the rulemaking. An NSRL does not require a business to test for the presence of glyphosate in California wines or any other products. In the Economic Impact Analysis for this rulemaking, OEHHA noted:

"One year after the date of listing, businesses that manufacture, distribute or sell products with glyphosate in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. *The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure*. (Emphasis added.)

Benefits of this regulation include sparing businesses the expense of calculating their own NSRL and possibly enabling them to reduce or avoid litigation costs..."

No changes were made based on this comment.

Comment #37 (Timothy Litzenburg): The single mouse study that OEHHA relied on was done by a glyphosate producer.

Response #37: Studies conducted or contracted by the chemical manufacturer often form part of the scientific data supporting carcinogenicity. As noted in the response to

comment #5, IARC found that two sets of studies in mice and six sets of studies in rats were adequate for the evaluation of glyphosate carcinogenicity. OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate in light of the requirement of Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met the criterion in Section 25703 as the most sensitive study of sufficient quality. No changes were made based on this comment.

Local Mandate Determination

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. Local agencies and school districts are exempt from Proposition 65. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. The regulation does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure.

Alternatives Determination

Pursuant to Government Code section 11346.5(a)(13), OEHHA initially determined that no reasonable alternative considered by OEHHA, or that has otherwise been identified and brought to the attention of OEHHA, would be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons than the proposed action, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law.

In accordance with Government Code section 11346.9(a)(4), OEHHA has considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed. OEHHA has also considered whether an alternative exists which would be as effective as and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective as and less burdensome to affected private persons than the proposed regulation. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed. The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The regulation does not create additional compliance requirements, but instead provides a "safe harbor" value that aids

businesses in determining whether a warning is required for a given exposure. The alternative to the proposed amendment to Section 25705(b) would be to not adopt an NSRL for the chemical. Failure to adopt an NSRL would leave the business community without a “safe harbor” level to assist businesses in complying with Proposition 65. Some commenters proposed alternative NSRLs and approaches for deriving an NSRL. These comments were not reasonable alternatives and are fully discussed in responses to comments within this FSOR. There were no small-business specific alternatives submitted during the rulemaking process.