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August 7, 2024

Via Electronic and U.S. Certified Mail

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**Re: Petition for Rulemaking to Clarify Section 24 of the Federal Insecticide,
Fungicide, and Rodenticide Act ("FIFRA"), 7 U.S.C. § 136v**

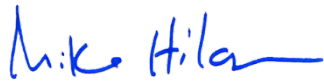
Dear Administrator Regan and Assistant Administrator Freedhoff:

The Attorneys General of the States of Nebraska, Iowa, Alabama, Arkansas, Georgia, Indiana, Louisiana, Montana, North Dakota, South Carolina, and South Dakota submit the enclosed petition to the United States Environmental Protection Agency ("EPA") to start rulemaking proceedings that will end the ongoing confusion as to the application of 7 U.S.C. § 136v with respect to additional labeling or packaging requirements arising under state law for products subject to FIFRA. Petitioners respectfully request EPA to declare that any state labeling requirements inconsistent with EPA's findings and conclusions from its human health risk assessment on human health effects, such as a pesticide's likelihood to cause cancer, birth defects, or reproductive harm, constitute misbranding under FIFRA.

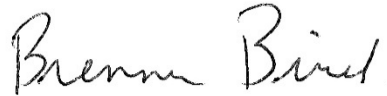
The issue presented by the enclosed Petition for Rulemaking is not new to EPA. The administrative record on this matter is extensive and well developed. Further, adopting the proposed rule would

not require additional technical review or study. The proposed rule merely seeks to clarify ambiguity concerning misbranding under FIFRA. Therefore, Petitioners respectfully request EPA to begin rulemaking within 90 days from the date of submission of this Petition.

Respectfully,



Mike Hilgers
Nebraska Attorney General



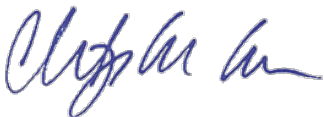
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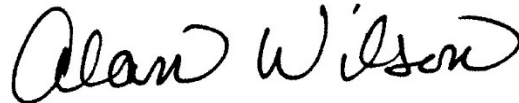
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Enclosures

BEFORE THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Submitted August 7, 2024

INTRODUCTION

The United States Environmental Protection Agency (“EPA”) has primary responsibility for implementing and enforcing the Federal Insecticide, Fungicide, and Rodenticide Act (“FIFRA”), 7 U.S.C. §§ 136 to 136y. FIFRA generally requires that EPA register pesticides and approve their labels before they may be distributed, sold, or used in any State. 7 U.S.C. § 136a. The label reviewed and approved by EPA is to control. States retain the power to restrict the sale or use of pesticides within their borders but cannot “impose or continue in effect any requirements for labeling or packaging in addition to or different from those required [under FIFRA].” 7 U.S.C. § 136v(b); *see id.* § 136v(a).

REQUESTED ACTION

Petitioners request that EPA initiate rulemaking to clarify the preemptive effect of registration decisions on state labeling requirements and common-law failure-to-warn claims. Petitioners urge EPA to amend 40 C.F.R. § 156.10 to clarify that statements or conclusions on FIFRA-registered products that are different from EPA's express findings and conclusions made during the product's registration review regarding the product's likelihood to cause cancer, birth defects, or reproductive harm shall be deemed false and misleading and thus preempted. In particular, any statements or representations on a label concerning a product's carcinogenic potential or other public-health risks that are different or not otherwise required by EPA constitute misbranding.

Specifically, Petitioners ask EPA to amend 40 C.F.R. § 156.10 “Labeling requirements” by inserting the following bold and underlined language in subsection (a)(5):

False or misleading statements. Pursuant to section 2(q)(1)(A) of the Act, a pesticide or a device declared subject to the Act pursuant to § 152.500, is misbranded if its labeling is false or misleading in any particular including both pesticidal and non-pesticidal claims. Examples of statements or representations in the labeling which constitute misbranding include:

- (i) A false or misleading statement concerning the composition of the product;
- (ii) A false or misleading statement concerning the effectiveness of the product as a pesticide or device;
- (iii) A false or misleading statement about the value of the product for purposes other than as a pesticide or device;
- (iv) A false or misleading comparison with other pesticides or devices;
- (v) Any statement directly or indirectly implying that the pesticide or device is recommended or endorsed by any agency of the Federal Government;
- (vi) The name of a pesticide which contains two or more principal active ingredients if the name suggests one or more but not all such principal active ingredients even though the names of the other ingredients are stated elsewhere in the labeling;
- (vii) A true statement used in such a way as to give a false or misleading impression to the purchaser;
- (viii) Label disclaimers which negate or detract from labeling statements required under the Act and these regulations;
- (ix) Claims as to the safety of the pesticide or its ingredients, including statements such as “safe,” “nonpoisonous,” “noninjurious,” “harmless” or “nontoxic to humans and pets” with or without such a qualifying phrase as “when used as directed”; and
- (x) Non-numerical and/or comparative statements on the safety of the product, including but not limited to:
 - (A) “Contains all natural ingredients”;
 - (B) “Among the least toxic chemicals known”
 - (C) “Pollution approved”

(xi) Statements or conclusions regarding the product’s human health effects, including the likelihood of causing cancer, birth defects, or reproductive harm, that are different from EPA’s findings and conclusions stated in its human health risk assessment conducted during the registration review of the product’s principal active ingredients.

IDENTITY AND INTEREST OF PETITIONERS

Petitioners are the States of Nebraska, Iowa, Alabama, Arkansas, Georgia, Indiana, Louisiana, Montana, North Dakota, South Carolina, and South Dakota.

Agriculture is vital in Petitioners' States. Last year, Nebraska and Iowa alone were home to 131,200 farms and ranches covering about 70 million acres. In Nebraska, farms and ranches cover 92 percent of the State's total land area. In 2023, Nebraska and Iowa farmers produced more than 4.2 billion bushels of corn and over 839 million bushels of soybeans, adding billions of dollars to the economy.¹ These farmers and the crops they grow help feed a growing population, contribute to rural, state, and national economies, and directly and indirectly employ millions of people. The pesticide products regulated under FIFRA are instrumental to these farmers' successes.

Among the products subject to FIFRA, glyphosate is particularly important for farmers in Petitioners' States. The advantages of glyphosate are well documented. Glyphosate controls 300 different weeds and can be applied directly to crops engineered to be glyphosate resistant. Using glyphosate, farmers can effectively manage weeds using fewer chemicals and other inputs. Better weed management also increases crop yields by allowing the growing crops to reach yield potential. Producing higher yields with fewer inputs benefits farmers in Petitioners' States, related industries, and downstream consumers.

Glyphosate's benefits for the environment are also well documented. Glyphosate, paired with glyphosate-resistant crops, encourages farmers to adopt conservation tillage. Conservation tillage reduces soil erosion and runoff from fields into the surface waters of Petitioners' States. Glyphosate is also less toxic and harmful than many other herbicides.

But Petitioners' interest in seeking uniformity by this rulemaking goes far beyond glyphosate. Glyphosate is merely the regulated pesticide that courts have considered in finding an ambiguity in FIFRA that the plain language of the statute does not support. The court-made gap in FIFRA's regulatory framework affects countless other pesticides and fungicides currently regulated under FIFRA, including some still being developed. The flawed analysis could have downstream effects for other federally regulated labeling requirements, such as poultry products under the Poultry Products Inspection Act and medical devices, food, and other substances subject to oversight by the Federal Drug Administration.

Further, Petitioners have a substantial interest in this rulemaking because state speech mandates, such as the warning label required by the State of California's Office of Environmental Health Hazard Assessment ("OEHHA"), are fundamentally at odds with Petitioners' consumer protection policies. Most States have adopted legal provisions prohibiting businesses from branding their products with false or misleading statements. Yet California is seeking to compel companies to display labels on their products that are inconsistent with, and contrary to, the long-held position of EPA, not to mention a broad list of international organizations and regulatory

¹ The statistics are drawn from the U.S. Department of Agriculture. See 2023 State Agriculture Overview: Nebraska, U.S. Dep't of Ag., <https://perma.cc/K8U5-2HG8> (May 24, 2024); 2023 State Agriculture Overview: Iowa, U.S. Dep't of Ag., <https://perma.cc/A7JS-NQNN> (May 24, 2024).

bodies. The Ninth Circuit recently enjoined enforcement of California’s labeling requirement as applied to glyphosate on First Amendment grounds. *See Nat’l Ass’n of Wheat Growers v. Bonta*, 85 F.4th 1263 (9th Cir. 2023). But the threat of labeling rules that differ by State, common-law failure-to-warn claims, and future, needless litigation continues.

As the entities charged with implementing and enforcing FIFRA, Petitioners also have an interest in a national, uniform standard for pesticide labeling under FIFRA. Congress was explicit in its intent for EPA’s registration decisions to be given primacy over labeling and packaging requirements arising under state law. Moreover, the court-created ambiguity in FIFRA relegates the work of EPA’s scientists to an afterthought despite their extensive time and expertise devoted to studying FIFRA-regulated products. If EPA does not act quickly to clarify its primacy over labeling, Petitioners and industry will be left to address state-imposed labeling obligations that differ from EPA’s long-held scientific findings in an area of law where Congress intended EPA to have the final word.

LEGAL FRAMEWORK

I. General Statutory and Regulatory Framework

FIFRA was enacted in 1947. *See* Federal Insecticide, Fungicide, and Rodenticide Act, Pub. L. No. 80-104, 61 Stat. 163 (1947). Under the original version of FIFRA, all pesticides sold in interstate commerce had to be registered with the Secretary of Agriculture. *Id.* § 6(c). The Secretary would register a pesticide if it complied with FIFRA’s labeling standards and was determined to be efficacious and safe. *Id.* In 1970, EPA assumed responsibility for this registration process. Reorganization Plan No. 3 of 1970, § 2(8)(i), 84 Stat. 2086, 2088 (July 9, 1970).

In 1972, Congress adopted extensive amendments to FIFRA, transforming it from a labeling law into a comprehensive regulatory regime. *See* Federal Environmental Pesticide Control Act of 1972, Pub. L. No. 92-516, 86 Stat. 973. “As amended, FIFRA regulated the use, as well as the sale and labeling, of pesticides; regulated pesticides produced and sold in both intrastate and interstate commerce; provided for review, cancellation, and suspension of registration; and gave EPA greater enforcement authority.” *Ruckelshaus v. Monsanto*, 467 U.S. 986, 991–92 (1984).

Before registering a pesticide for sale in the United States, EPA first “determine[s] that the pesticide will not cause ‘unreasonable adverse effects on the environment,’” including potential carcinogenicity. *Id.* (quoting 7 U.S.C. § 136a(c)(5)(C)); *see also* 7 U.S.C. §§ 136(j), 136a(d)(1)(C). EPA analyzes voluminous scientific data before making a registration determination. FIFRA also requires EPA to review a pesticide’s registration, including its effect on human health, at least every 15 years. 7 U.S.C. § 136a(c)(1)(F)(ii)(II), (g)(1)(A)(i), (g)(1)(A)(iv).

Under FIFRA, a manufacturer seeking to register a pesticide must also submit a proposed label to EPA and certain supporting data. *See id.* § 136a(c)(1)(C), (F). EPA will register the pesticide if it determines that the pesticide is efficacious, will not cause unreasonable adverse effects on humans and the environment, and its label complies with the statute’s prohibition on misbranding. *See id.* § 136a(c). A pesticide is “misbranded” if its label contains a statement that is “false or misleading in any particular,” including a false or misleading statement related to the

pesticide's efficacy. 7 U.S.C. § 136(q)(1)(A); 40 C.F.R. § 156.10(a)(5)(ii). A pesticide is also misbranded if its label does not contain adequate instructions for use or omits necessary warnings or cautionary statements. 7 U.S.C. § 136(q)(1)(F), (G).

It is unlawful under FIFRA to sell a pesticide that is registered but misbranded. *See* 7 U.S.C. § 136j(a)(1)(E). Selling a misbranded product subjects a registrant to civil and criminal liability. *Id.* § 136l. Additionally, manufacturers must report incidents involving a pesticide's toxic effects that may not be adequately reflected in its label's warnings. 40 C.F.R. § 159.184(a), (b). EPA may institute cancellation proceedings and take other enforcement action if it determines that a registered pesticide is misbranded. *See* 7 U.S.C. § 136d(b).

FIFRA also contemplates the States playing a role in pesticide regulation. *See* 7 U.S.C. § 136v. In the case of most environmental programs, Congress typically delegates power to an agency, such as the EPA, to develop and implement the program through regulation. EPA may then delegate implementation to individual States. Once delegated, a State becomes the primary entity for implementing and enforcing the program. FIFRA fits this typical pattern. It authorizes a State to regulate the sale or use of any federally registered pesticide or device in the State, but only if and to the extent that the regulation does not permit any sale or use prohibited by FIFRA. *Id.* § 136v(a).

Unlike other environmental programs, however, FIFRA prohibits States from enacting more stringent or even different labeling requirements than those imposed by EPA. Section 136v(b), titled "Uniformity," provides that States "shall not impose or continue in effect any requirements for labeling or packaging in addition to or different from those required under this subchapter." *Id.* § 136v(b). Thus, a State may not impose different, additional, or more stringent labeling requirements than those imposed by federal law. The Supreme Court has held that the term "requirements" in § 136v(b) reaches beyond statutes and regulations to embrace common-law duties if those duties require manufacturers to label or package their products in a particular way. *Bates v. Dow Agrosciences L.L.C.*, 544 U.S. 431, 443–44 (2005).

II. Evolution of Misbranding under FIFRA

Numerous cases have looked at FIFRA preemption of state law liability claims. Those cases generally focus on whether the state claims are based on allegedly inadequate labeling rather than alleged violations of state sale or use requirements of pesticides. Before *Bates*, the federal courts in the First, Fourth, Fifth, Seventh, Eighth, Ninth, Tenth, and Eleventh Circuits concluded that § 136v(b) preempted state common-law failure-to-warn or inadequate labeling claims.²

In 2005, the Supreme Court found that failure-to-warn claims arising under state tort law constitute "requirements for labeling or packaging," thus implicating FIFRA's preemption provision. *Bates*, 544 U.S. at 446. But FIFRA preempts state tort law only if state law requires

² *See e.g. Taylor AG Indus. V. Pure-Gro*, 54 F.3d 555, 560 (9th Cir. 1995); *Bice v. Leslie's Poolmart, Inc.*, 39 F.3d 887, 888 (8th Cir. 1994); *MacDonald v. Monsanto Co.*, 27 F.3d 1021, 1024–25 (5th Cir. 1994); *Worm v. Am. Cyanamid Co.*, 5 F.3d 744, 747 (4th Cir. 1993); *King v. E.I. Dupont De Nemours & Co.*, 996 F.2d 1346, 1349 (1st Cir. 1993); *Shaw v. Dow Brands Inc.*, 994 F.2d 364, 371 (7th Cir. 1993); *Ark.-Platte & Gulf P'ship v. Van Waters & Rogers, Inc.*, 981 F.2d 1177, 1179 (10th Cir. 1993).

labeling “in addition to or different from” the labeling and packaging requirements of FIFRA. *Id.* at 447. The Supreme Court adopted a “parallel requirements” reading of § 136v(b), holding that a state-law labeling requirement is *not* preempted by § 136v(b) if it is equivalent to and consistent with FIFRA’s misbranding provisions. *Id.*

Under *Bates*’s “equivalency” test, a state-law labeling requirement must equal FIFRA’s labeling requirement and “must also be measured against any relevant EPA regulations that give content to FIFRA’s misbranding standards.” 544 U.S. at 453. As the Court observed, “[a]t present, there appear to be relatively few regulations that refine or elaborate upon FIFRA’s broadly phrased misbranding standards. To the extent that EPA promulgates such regulations in the future, they will necessarily affect the scope of preemption under § 136v(b).” *Id.* at 453 n.28.

Since *Bates*, two courts of appeals have considered whether FIFRA’s labeling requirement preempts other state common-law claims. The Ninth Circuit applied the preemption framework established in *Bates* to a failure-to-warn claim under California common law brought against a pesticide manufacturer for a product containing glyphosate. *See Hardeman v. Monsanto Co.*, 997 F.3d 941 (9th Cir. 2021). It decided that the failure-to-warn claim constituted a “requirement for labeling or packaging” under § 136v(b), thus satisfying the first prong of the preemption analysis. *Id.* at 955. But the court held that California’s duty to warn and FIFRA’s misbranding provision were equivalent and consistent with one another, such that state law did not impose a requirement “in addition to or different from” FIFRA’s labeling requirements. *Id.* at 955–56. The court stated that “only where there is a relevant EPA action *carrying the force of law* are state failure-to-warn claims prohibited from imposing requirements inconsistent with that action.” *Id.* at 957. According to the Ninth Circuit, EPA’s registration of a product raises only a “rebuttable presumption” that the pesticide and its label comply with FIFRA but does not itself carry the force of law and does not preempt state law. *Id.*

Similarly, the Eleventh Circuit recently considered whether a plaintiff’s failure-to-warn claim against a pesticide manufacturer for a product containing glyphosate was preempted by FIFRA. *Carson v. Monsanto Co.*, 92 F.4th 980 (2024). The court held that FIFRA did not preempt the claim because Georgia’s common law and FIFRA’s labeling requirements are consistent, even if not identical. *Id.* at 992–93. The Eleventh Circuit concluded that EPA’s registration of a pesticide was not an agency action that counted as a “requirement” under FIFRA because the FIFRA registration process lacked the formality of notice-and-comment rulemaking or formal adjudication. *Id.* at 993. The court, however, did not foreclose the possibility that formal EPA action—like the rulemaking requested here—would receive preemptive effect. *See id.* The deadline to file a petition for certiorari has not yet expired in that case.

Neither the Ninth Circuit nor the Eleventh Circuit gave weight to EPA’s own conclusion that state labeling requirements constitute misbranding. On August 7, 2019, EPA issued a letter to manufacturers expressly disagreeing with the International Agency for Research on Cancer’s (“IARC”) classification of glyphosate as “probably carcinogenic to humans.” The 2019 letter was prompted by California’s efforts to require that a Proposition 65 warning label be placed on glyphosate products. The 2019 letter notes that, based on EPA scientists’ independent evaluation of available data since the IARC classification, EPA had concluded that glyphosate is “not likely to be carcinogenic to humans.” Letter from Michael L. Goodis, Director of EPA’s Registration

Division (Aug. 7, 2019), <https://perma.cc/W42T-GW7N>. Given this independent determination and its consistency with several other international expert panels and regulatory authorities, EPA concluded state labeling laws requiring a statement that glyphosate may cause cancer is false and misleading and thus violates FIFRA’s misbranding provision.

The Ninth Circuit dismissed EPA’s position, concluding that the 2019 letter was not subject to formal administrative rulemaking procedures and therefore lacked the force of law to preempt the California failure-to-warn claim. *Hardeman*, 997 F.3d at 957–58; *see also Carson*, 92 F.4th at 998 (reading letter narrowly). The pesticide manufacturer in *Hardeman* petitioned the U.S. Supreme Court for a writ of certiorari. Petition for Writ of Certiorari, *Monsanto Co. v. Hardeman*, 142. S. Ct. 2834 (No. 21-241) (mem.). The United States filed an amicus brief opposing certiorari. The United States admitted that its position was a complete reversal from the position it took in its Ninth Circuit amicus brief because of a “change in Administration.” Brief for the United States as Amicus Curiae Opposing Certiorari at 6, *Hardeman*, 142. S. Ct. 2834 (No. 21-241).

The brief opposing certiorari acknowledged that “EPA has long concluded that glyphosate is not likely to be carcinogenic to humans and has repeatedly articulated that view in registration decisions spanning decades.” *Id.* at 12. According to the United States, mere inconsistency between state and federal risk assessments alone does not preempt enforcement of state tort law:

EPA could—either through rulemaking or through some other regulatory action carrying the force of law—make a binding determination that the labels of pesticides containing glyphosate should not contain cancer warnings. Such a determination would preempt any state law tort claim premised on a manufacturer’s failure to provide such warnings. But neither EPA’s repeated statements that glyphosate is unlikely to be carcinogenic to humans, nor its approval of pesticide labeling without cancer warnings, imposes any such prohibition.

Id. at 13. Petitioners ask that EPA do just that—give its scientific findings and conclusions preemptive effect.

GROUND FOR REQUESTED RULEMAKING

Courts and States should not be allowed to undermine EPA’s risk assessments under FIFRA. With its knowledge and expertise on FIFRA-regulated products, EPA should stand with its scientists and use its rulemaking authority to formally codify the preemptive effect of its risk assessment findings about FIFRA labeling. EPA’s regulations that implement FIFRA already require that a label include EPA’s toxicity findings and EPA’s required “signal” word for toxicity categories. The same should hold true for EPA’s other health-related findings.

The confusion over glyphosate is an excellent example of the problems that may arise if EPA does not engage in rulemaking to clarify the preemptive nature of its scientific findings and conclusions. In its amicus brief to the Ninth Circuit in *Hardeman*, filed December 20, 2019, the United States explains:

The potential that glyphosate is carcinogenic to humans is not something that EPA has ignored. EPA has studied and expressly addressed the carcinogenic potential of glyphosate a number of times over the past three decades. And EPA continues to assess it. Through FIFRA, Congress determined that EPA should make these scientific judgments for the nation as a whole. States may, of course, restrict or prohibit the sale or use of pesticides in the State if they disagree with EPA's assessment. But States are prohibited from second-guessing EPA's determination of what risks should be reflected on pesticide labeling.

Brief for the United States as Amicus Curiae Supporting Monsanto Co. at 20, *Hardeman*, 997 F.3d 941 (No. 19-16636) (citations omitted).

Since 2009, EPA has been reviewing its registration of glyphosate under FIFRA. *See* EPA-HQ-OPP-2009-0361. In May 2019, EPA published its interim registration review decision for glyphosate in the Federal Register, which summarized EPA's proposed conclusions weighing the costs and benefits of glyphosate and setting forth specific proposed label requirements. *See* Glyphosate Proposed Interim Registration Review Decision; Notice, 84 Fed. Reg. 19,782 (May 6, 2019). On January 22, 2020, the Interim Decision was signed by EPA. *See* EPA, Glyphosate: Interim Registration Review Decision, Case No. 0178 (Jan. 22, 2020). As to human health, EPA "thoroughly evaluated potential human health risk associated with exposure to glyphosate and determined that there are no risks to human health from the current registered uses of glyphosate and that glyphosate is not likely to be carcinogenic to humans." *Id.* at 10.

The Rural Coalition and the Natural Resources Defense Council filed petitions for review in the Ninth Circuit challenging the findings of EPA's Interim Decision on glyphosate registration. *See Nat. Res. Def. Council v. EPA (NRDC)*, 38 F.4th 34 (9th Cir. 2022). The petitioners there, like California with its Proposition 65 efforts, held up the findings of the IARC and asserted that IARC's carcinogenicity findings should be given credence.

On May 18, 2021, EPA submitted its brief on appeal, providing a detailed description of the Agency's historical study of glyphosate. Brief for EPA, *NRDC*, 38 F.4th 34 (9th Cir. 2022) (Nos. 20-70787, 20-70801). EPA vigorously defended its own scientists' conclusions that glyphosate did not pose any risks of concern. *Id.* at 30–39. EPA expressly noted that, although the IARC characterized glyphosate as "probably carcinogenic to humans" in 2015, every other agency and organization that has recently conducted a scientific review of glyphosate has concluded that glyphosate does not pose a likely risk of cancer in humans. *Id.* at 32. Finally, EPA expressly addressed IARC's findings and explained why EPA's conclusion was both more robust and transparent than IARC's analysis. *Id.* at 33–39.³

Congress intended EPA to be the preeminent authority on the health effects of products registered under FIFRA. Petitioners respectfully request that EPA start rulemaking to prevent

³ The Ninth Circuit ultimately vacated EPA's interim decision to register glyphosate. 38 F.4th at 40. EPA subsequently withdrew its interim decision stated that it anticipates issuing a final registration review for glyphosate in 2026. Memorandum from Cathryn Britton, Branch Chief of Risk Management and Implementation Branch in the Pesticide Re-evaluation Division of EPA 1, 6 (Sept. 21, 2022).

courts and regulatory agencies from engaging in backdoor challenges to EPA's conclusions and creating a patchwork of labeling requirements across the country.

Though the Ninth Circuit incorrectly held in *Hardeman* that FIFRA does not preempt California's Proposition 65, the Ninth Circuit recently found that Proposition 65 runs into a separate legal barrier: the First Amendment. The court concluded that California's requirement that glyphosate contain a warning that it is known to cause cancer constituted compelled commercial speech on a contested and controversial matter that does not survive intermediate scrutiny. *Nat'l Ass'n of Wheat Growers v. Bonta*, 85 F.4th 1263, 1266–67 (9th Cir. 2023). The Ninth Circuit thus permanently enjoined California from enforcing Proposition 65 as applied to glyphosate labeling. *Id.* at 1283. But the opinion leaves the door open for California to try again, if it can muster a label requirement that is "purely factual." *See id.* at 1276–80. And the opinion says nothing about the status of state law failure-to-warn claims, which do not compel commercial speech.

EPA can avoid the onslaught of litigation and continual review of state labeling requirements if it proceeds with Petitioners' requested rulemaking. EPA has authority and needs to adopt a rule clarifying that any statements on a product's carcinogenic potential or other public-health risks not otherwise required by EPA labeling under FIFRA constitute misbranding. The Supreme Court raised the ambiguity as to the preemptive nature of EPA's labeling requirements in *Bates*: "At present, there appear to be relatively few regulations that refine or elaborate upon FIFRA's broadly phrased misbranding standards. To the extent EPA promulgates such regulations in the future, they will necessarily affect the scope of preemption under § 136v(b)." *Bates*, 544 U.S. at 453 n.28. The lack of clarity was also acknowledged by the Third Circuit in *Indian Brand Farms, Inc. v. Novartis Crop Protection, Inc.*, 617 F.3d 207, 222 (3rd Cir. 2010) (citing *Bates*, 544 U.S. at 453, n.28). The Ninth Circuit's decision in *Hardeman* raises the concern as well. *See* 997 F.3d at 958 ("because EPA's actions—such as registering Roundup, approving Roundup's label, and issuing the 2019 letter—do not have the force of law" there is no preemption of state-law claims for failure to warn).

Since 2005, courts have signaled to EPA the need to engage in rulemaking on this issue. Nearly 20 years later, the problem has not been addressed. Petitioners respectfully request that action be taken now.

CONCLUSION

For these reasons, Petitioners request that EPA initial rulemaking to codify the preemptive effects of its scientific findings developed during the registration process as they relate to health warnings mandated by state law or under common law failure-to-warn claims. The courts and the Department of Justice have consistently observed the authority of EPA to do so. The basis and support for the requested rulemaking is already well developed and does not require EPA to engage in additional technical review or study. Petitioners therefore request that EPA issue the proposed rule for public comment within 90 days of submission of this Petition.

BEFORE THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

**IN RE: PETITION FOR
RULEMAKING TO
CLARIFY SECTION 24 OF
THE FEDERAL
INSECTICIDE, FUNGICIDE,
AND RODENTICIDE ACT
("FIFRA"), 7 U.S.C. § 136v**

Submitted August 7, 2024

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Exhibit 1



Glyphosate

Proposed Interim Registration Review Decision Case Number 0178

April 2019

Approved by: _____

Charles "Billy" Smith
Acting Director
Pesticide Re-evaluation Division

Date: _____

4/23/19

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I. INTRODUCTION

This document is the Environmental Protection Agency's (the EPA or the agency) *Proposed Interim Registration Review Decision* (PID) for glyphosate acid and its various salt forms (PC Codes 103601, 103604, 103605, 103607, 103608, 103613, and 417300, case 0178), and is being issued pursuant to 40 CFR § 155.56 and 155.58. A registration review decision is the agency's determination whether a pesticide continues to meet, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The agency may issue, when it determines it to be appropriate, an Interim Registration Review decision before completing registration review. Among other things, the Interim Registration Review Decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review case. Additional information on glyphosate can be found in the EPA's public docket (EPA-HQ-OPP-2009-0361) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by the EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided as <http://www2.epa.gov/pesticide-reevaluation>. In 2006, the agency implemented the registration review program pursuant to FIFRA § 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

The EPA is issuing a PID for glyphosate so that it can (1) move forward with aspects of the registration review case that are complete and (2) implement interim risk mitigation (see Appendices A, B, and C). The agency is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (together, the Services) to develop methodologies for conducting national threatened and endangered (listed) species assessments for pesticides in accordance with the Endangered Species Act (ESA) § 7. Therefore, although the EPA has not yet fully evaluated risks to listed species, the agency will complete its listed species assessment and any necessary consultation with the Services for glyphosate prior to completing the glyphosate's registration review. Likewise, the agency will complete endocrine screening for glyphosate, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), before completing registration review. Last, the EPA will determine whether pollinator exposure and effects data are necessary to make a final registration review decision for glyphosate and issue a data call-in (DCI) to obtain any such data prior to completing the glyphosate registration review case. See Appendices D and E, respectively, for additional information on the listed species assessment and the endocrine screening for the glyphosate's registration review.

The glyphosate registration review case covers glyphosate acid (PC code 417300) and the following salt forms with active pesticide registrations: isopropylamine salt (pc code 103601), ammonium salt (PC code 103604), ethanol amine salt (PC code 103605), diammonium salt (PC code 103607), dimethyl ammonium salt (PC code 103608), and the potassium salt (PC code 103613). Glyphosate is a non-selective, systemic herbicide registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, cereal grains, and other field crops. Non-agricultural uses include residential spot treatments, aquatic areas, forests, rights of ways, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land. Glyphosate is also registered for use on glyphosate-resistant crops such as alfalfa, corn, soybean, cotton, canola, and sugar beets. The first pesticide product containing glyphosate was registered in 1974; a Reregistration Eligibility Decision (RED) for glyphosate was completed in 1993. Since then, the EPA has reviewed the risk assessments for glyphosate to determine if updates were necessary when new uses were added to glyphosate labels.

This document is organized in five sections: the *Introduction*, which includes this summary and a summary of public comments and the EPA's responses; *Use and Usage*, which describes how and why glyphosate is used and summarizes data on its use; *Scientific Assessments*, which summarizes the EPA's risk and benefits assessments, updates or revisions to previous risk assessments, and provides broader context with a discussion of risk characterization; the *Proposed Interim Registration Review Decision*, which describes the mitigation measures proposed to address risks of concern and the regulatory rationale for the EPA's proposed interim registration review decision; and, last, the *Next Steps and Timeline* for completion of this registration review.

A. Summary of Glyphosate's Registration Review

Pursuant to 40 CFR § 155.50, the EPA formally initiated registration review for glyphosate with the opening of the registration review docket for the case. The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of glyphosate.

- July 2009 - The *Glyphosate Preliminary Work Plan (PWP)*, Human Health Scoping Document, and Environmental Fate and Effects Problem Formulation were posted to the docket for a 60-day public comment period.
- December 2009 - The *Glyphosate Final Work Plan (FWP)* was issued. Comments received on the PWP covered the following topics: opposition to the use of glyphosate, the toxicity of glyphosate formulations and inert ingredients, use and usage trends, human health risks, ecological risks, endocrine disruption, and the benefits of glyphosate. The public comments received did not change the schedule, risk assessment needs, or anticipated data requirements in the FWP.
- September 2010 - A Generic Data Call-In (GDCI) for glyphosate was issued for data needed to conduct the registration review risk assessments. All required data were

submitted and reviewed. The registration review GDCI for glyphosate is considered satisfied.

- December 2016 – The agency convened a FIFRA Scientific Advisory Panel meeting to consider and review a set of scientific issues related to the EPA’s evaluation of the carcinogenic potential of glyphosate. The meeting agenda, the agency’s cancer issue paper, charge questions for the panel, transcript, and final report are available on EPA’s website: <https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel>. Additional supporting materials and comments received from the public can be found in docket EPA-HQ-OPP-2016-0385 at www.regulations.gov.
- December 2017 – The agency published the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (dated December 12, 2017), the *Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate* (dated December 12, 2017), the *Glyphosate Draft Human Health Risk Assessment for Registration Review* (dated December 12, 2017), the *Registration Review – Preliminary Ecological Risk Assessment for Glyphosate and its Salts* (dated September 8, 2015) online (<https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate>).
- February 2018 - The agency announced the availability of the human health and ecological risk assessments for a 60-day public comment period. Over 238,000 comments were received during the comment period, most of which came from various mass mail campaigns. Approximately 2,244 unique submissions were received from various stakeholders, including pesticide registrants, industry groups, farmers, grower groups, private citizens, non-governmental organizations, states, and the US Department of Agriculture (USDA). These comments and the agency’s responses are summarized below. The comments did not change the risk assessments or registration review timeline for glyphosate.
- September 2018 – The Environmental Working Group, joined by Ben & Jerry’s Homemade, Inc., Happy Family Organics, MegaFood, MOM’s Organic Market, National Co+op Grocers, Nature’s Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farm, Inc. submitted a petition to the agency. The petition requested that the EPA lower the tolerance for oats and explicitly prohibit preharvest use on oats on glyphosate US labels. The agency is still reviewing this petition and has issued a Federal Register Notice of Filing for public comment in docket EPA-HQ-OPP-2019-0066. The agency intends to respond to this petition concurrently with the issuance of the *Interim Registration Review Decision* for glyphosate.
- March 2019 - The agency is now announcing the availability of the *Proposed Interim Registration Review Decision* (PID) in the docket for glyphosate, for a 60-day public comment period. Along with the PID, the following documents are also posted to the glyphosate docket:

- *Glyphosate: Response to Comments, Usage, and Benefits* (dated April 18, 2018)
- *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* (dated April 23, 2019)
- *Response to Public Comments on the Preliminary Ecological Risk Assessment for Glyphosate* (dated November 21, 2018)

B. Updates Since the Issuance of the Glyphosate Risk Assessments

The Agency received on September 27, 2018 a petition from the Environmental Working Group, Ben & Jerry's Homemade, Inc., Happy Family Organics, MegaFood, MOM's Organic Market, National Co-op Grocers, Nature's Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farms, Inc. The petitioners request that the agency reduce the tolerance of the pesticide glyphosate in or on oats from 30 ppm to 0.1 ppm and modify labels to explicitly prohibit preharvest use on oats. The petitioners assert that the current tolerance level for oat is not protective enough when taking into consideration the actual dietary exposure to glyphosate in oats and the potential carcinogenicity of glyphosate. The agency is still reviewing this petition. Since this petition was submitted outside of the public comment period for the human health and ecological risk assessments, which closed on April 30, 2018, EPA has not considered it as a public comment on the risk assessments in preparation of this Proposed Interim Registration Review Decision. However, the Agency will treat this petition as a public comment on this Proposed Interim Registration Review Decision; a copy of the petition will be posted to the glyphosate registration review docket. The EPA intends to address this petition concurrently with the development of the Interim Registration Review Decision for glyphosate, taking into consideration issues raised in the petition and any comments the agency receives on its Notice of Filing.

In accordance with FFDCA section 408(d)(3), EPA is publishing EWG's petition for public comment; the public comment period will close 30 days after publication. The full petition is posted in docket EPA-HQ-OPP-2019-0066 at www.regulations.gov. This Proposed Interim Decision reflects the conclusions of EPA's most recent risk assessments and does not address the claims raised in the petition.

C. Summary of Public Comments on the Draft Risk Assessments and Agency Responses

During the 60-day public comment period for the glyphosate preliminary risk assessments, which opened on February 27, 2018 and closed on April 30, 2018, the agency received 238,290 comments. Approximately 2,244 unique submissions were received from various stakeholders, including glyphosate registrants, grower groups, non-governmental organizations, pesticide industry groups, states, and the US Department of Agriculture. Most comments came from mass mail campaigns, and approximately 200 substantive comments were received from various stakeholders. Comments relating to widespread concerns, comments of a broader regulatory nature, and the agency's responses to those comments are summarized below. Due to the high volume of comments received for glyphosate, the agency has combined comments by topic instead of responding to individual stakeholders and has focused its responses on comments that have not been addressed previously via the FIFRA SAP meeting or in previous registration

review documents for glyphosate. The comments did not result in changes to the agency's risk assessments. The agency thanks all commenters for their comments and has considered them in developing this PID.

For more detailed responses to comments relating to the human health risk assessment, see the *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment*. For more detailed responses to comments relating to the ecological risk assessment, see the *Response to Public Comments on the Preliminary Ecological Risk Assessment for Glyphosate*. For detailed responses to comments on the use/usage of glyphosate and the benefits, see the *Glyphosate: Response to Comments, Usage, and Benefits*. All responses to comments documents are available in the public docket for glyphosate.

Comments About the EPA's Cancer Evaluation:

Many commenters expressed disagreement with the EPA's cancer conclusion, citing the International Agency for Research on Cancer's (IARC's) 2015 classification of glyphosate as "probably carcinogenic to humans." Comments were also received regarding the EPA's weight of evidence evaluation of the animal carcinogenicity data.

The EPA Response: The EPA conducted an independent evaluation of the carcinogenic potential of glyphosate and has determined that glyphosate is "not likely to be carcinogenic to humans." The agency's cancer classification is based on a thorough weight-of-evidence review of all relevant data and is in accordance with the agency's 2005 *Guidelines for Carcinogen Risk Assessment*.¹ The agency presented its draft cancer evaluation to the FIFRA Scientific Advisory Panel (SAP) in December 2016. Although the SAP did not reach consensus on several questions, none of the panelists believed that glyphosate should be classified as "likely to be carcinogenic to humans" or "carcinogenic to humans." Given the variety of opinions expressed, the agency revised its cancer evaluation and addressed comments from the SAP where consensus appeared to be reached. EPA's full weight-of-evidence evaluation can be found in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, available in the glyphosate public docket (EPA-HQ-OPP-2009-0361).

Comments received from stakeholders concerning the weight of evidence evaluation were previously addressed in the *Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate* (also available in the glyphosate public docket).

EPA's cancer evaluation is more robust than IARC's evaluation. IARC's evaluation only considers data that have been published or accepted for publication in the openly available scientific literature. As a result, IARC only considered a subset of the studies included in the EPA's evaluation. For instance, IARC only considered 8 animal carcinogenicity studies while the agency used 15 acceptable carcinogenicity studies in its evaluation. The EPA also excluded some studies that were not appropriate for determining the human carcinogenic potential of glyphosate, such as studies in non-mammalian species (*i.e.*, worms, fish, reptiles, and plants) which IARC used in its evaluation.

¹ <https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment>

The Agency's cancer evaluation for glyphosate is also more transparent. EPA's draft cancer evaluation was presented to a FIFRA SAP for external peer review. EPA solicited public comment on the carcinogenic potential of glyphosate as part of the SAP process, which is well-documented with an agenda, transcript, meeting notes, and final SAP report. EPA responded to the SAP report, addressed panel recommendations, and made revisions to its cancer assessment that were transparent and provided to the public. EPA also solicited public comment on its full human health and ecological risk assessment for glyphosate in February 2018. In contrast, IARC meetings are not accessible to the public. Its deliberations are closed, its process does not allow for public comments to be submitted for consideration, there are no materials provided in advance of the meeting, and IARC's reports are final without an external peer review.

The EPA has not identified any new information received during the public comment period which ended on April 30, 2018 that would result in changes to the conclusion of its cancer assessment. The agency's cancer conclusion is consistent with other regulatory authorities and international organizations, including the Canadian Pest Management Regulatory Agency, the Australian Pesticide and Veterinary Medicines Authority, the European Food Safety Authority, the European Chemicals Agency, the German Federal Institute for Occupational Safety and Health, the Joint FAO/WHO Meeting on Pesticide Residues, the New Zealand Environmental Protection Authority, and the Food Safety Commission of Japan.

Comments on the EPA's Use of Open Literature Studies:

Many commenters asserted that the EPA relies too heavily on industry-funded studies and that these studies are not accessible to the public. Commenters requested that the EPA use open literature studies to assess glyphosate and point to various open literature studies describing various human health and ecological effects.

The EPA Response: The EPA requires a substantial amount of data to be collected and submitted for pesticide registration and registration review (see 40 CFR part 158 data requirements, <https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration>). The required data provide a wide range of information and include the following: product chemistry, product performance, studies that determine hazard to humans and domestic animals, studies that determine hazard to non-target organisms, post-application exposure studies, applicator/user exposure studies, pesticide spray drift studies, environmental fate, and residue chemistry studies. Although many of these studies are submitted by pesticide producers, the EPA has rigorous guidelines for how studies should be conducted (<https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/master-list-test-guidelines-pesticides-and-toxic>). The agency independently evaluates required studies for scientific acceptability. Laboratories conducting studies must address Good Laboratory Practices (GLP) designed to ensure data quality and integrity. The EPA's Office of Enforcement and Compliance Assurance (OECA) periodically inspects labs that conduct required studies to ensure that labs are in compliance with GLP regulations.

When studies are submitted to the agency for review, test reports must summarize and supply all the individual data obtained as part of the study. An independent evaluation is prepared for each study and a Data Evaluation Record (DER) is generated to summarize the study methods, results, and conclusions. DERs are subject to an internal peer review process and scientific review

committees within the Office of Pesticide Programs to ensure accuracy and consistency of interpretation prior to finalization.

Registrant-submitted studies are proprietary, and under FIFRA, cannot be released to any representative of a multinational pesticide producer or to anyone who intends to deliver such information to a multinational pesticide producer. Anyone not associated with a multinational pesticide producer may file Freedom of Information Act (FOIA) requests to access studies evaluated by the agency. For information on how to submit FOIA requests to access certain glyphosate studies, visit the EPA's website: <https://www.epa.gov/foia/foia-request-process>.

The EPA also reviewed the open literature to conduct both human health and ecological risk assessments.

The open literature review conducted for human health risk assessment is described in the document *Glyphosate—Systematic Review of Open Literature*. For its cancer evaluation, the EPA conducted an additional fit-for-purpose systematic review to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate. This additional review is described in the agency's *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* which is available in the public docket. The extensive list of journal citations provided by some commenters was screened for new studies not previously considered in the EPA's search of the open literature and did not turn up any studies that would impact the conclusions the EPA reached in its human health risk assessment.

The open literature data evaluated for ecological risk assessment is described in the agency's *Registration Review – Preliminary Ecological Risk Assessment for Glyphosate and its Salts* and also in *Appendix G Bibliography of Ecotox Papers*. The extensive list of journal citations provided by some commenters was screened for potential new information relevant to the ecological risk assessment. The information submitted generally support the conclusions the EPA reached in its ecological risk assessment and do not warrant any changes.

The EPA's criteria for evaluating open literature data for both human health and ecological risk assessment are available online (<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-selecting-and-evaluating-open>).

Comments on Glyphosate Residues in Foods and Beverages:

Many commenters pointed to reports of glyphosate residues being detected in food/beverage commodities such as cereal, wine, orange juice, and others and express concerns about consumer safety. Others pointed to use of glyphosate as a pre-harvest desiccant for wheat as a source of glyphosate residues in cereal products.

The EPA Response: The EPA is aware of reports of glyphosate residues being detected in various foods and beverages. Due to its widespread use, trace amounts of glyphosate residues may be found in various food/beverage commodities. However, these trace amounts are below maximum residue levels established by the agency for those commodities and are not expected to pose risks of concern to consumers. For example, EPA has received results of testing of glyphosate residues in orange juice at a maximum of 26 parts per billion (ppb). At this

concentration, a 10 kg child would have to consume approximately 385 liters of orange juice every day to reach the chronic reference dose of 1 mg/kg/day (the maximum acceptable oral dose that is the threshold of concern).

EPA evaluated dietary exposure to all population subgroups, including children, infants, and women of child-bearing age. There were no dietary risks of concern for glyphosate using an unrefined analysis, which (1) assumes that all food commodities contain maximum legal residues (*i.e.*, tolerance-level residues) and all registered food crops have been treated with glyphosate, and (2) uses high-end estimates of glyphosate in drinking water.

Commenters point to the use of glyphosate as a pre-harvest desiccant for wheat as a source of glyphosate residues in cereal products. The wheat desiccant use was considered in the agency's dietary risk assessment; EPA assumed maximum legal residues in wheat and other cereal grains. Taking exposures from those residues into consideration in its most recent human health risk assessment, EPA's estimation of risk from aggregate exposure to glyphosate, even including residues from pre-harvest desiccant use on wheat, is below the agency's level of concern. However, the agency has received a petition from the Environmental Working Group concerning the tolerance for oats and pre-harvest use on oats for which the agency is taking public comment. Additional information is described in section I.B of this document.

Comments on Formulations Toxicity:

Many commenters expressed concerns that glyphosate formulations are more toxic than glyphosate alone and questioned the toxicity of inert ingredients and the lack of transparency for inert ingredients and other contaminants in pesticide products.

The EPA Response: Most pesticide products contain substances in addition to the active ingredient (known as inert ingredients) which aid in the performance and effectiveness of the pesticide product. All active and inert ingredients must be approved by the agency when a pesticide product is first registered, including for glyphosate products. Since there are over 500 glyphosate products registered at different times in the US, the agency has assessed new inert ingredients at multiple points over the years for different formulations of glyphosate. The EPA evaluates the active and inert ingredients' hazard potential (*i.e.*, toxicity) with a battery of toxicity data. Any contaminants or impurities associated with formulation components must be reported to the agency and evaluated on a case-by-case basis. The agency reviews the amount in the formulation, the manufacturing information, and information on what steps are taken to limit or remove impurities. EPA can require that any inert ingredients of toxicological concern be listed in the ingredients statement of the label if determined to pose a hazard to humans or the environment (CFR § 156.10(g)(7)).

Glyphosate has been studied in a multitude of studies, including on multiple formulations that contain glyphosate. All studies of adequate scientific caliber that the Agency was aware of were incorporated into the risk assessment. For the glyphosate ecological risk assessment, ecotoxicity data on glyphosate formulations were reviewed in addition to data on glyphosate alone and relevant studies were summarized in the *Registration Review – Preliminary Ecological Risk Assessment for Glyphosate and its Salts*.

For human health risk assessment, the EPA searched the open literature to find glyphosate formulations toxicity data but there are few research projects that have attempted to directly compare technical grade glyphosate to the formulations under the same experimental design. Furthermore, there are even fewer instances of studies comparing toxicity across formulations. Most studies using commercial formulations identified as part of EPA's review were *in vitro* studies, which are difficult to translate into *in vivo* effects where metabolism and clearance would play a large role in potential toxicity. EPA gave *in vivo* studies greater weight, however none of the *in vivo* studies with commercial formulations were found to be of adequate quality for use in human risk assessment. Common limitations observed in *in vivo* formulations studies include: lack of test material information, exposure conditions not adequately described/documented, data were presented only as graphs and measures of variability were not included, samples sizes were too small or not reported, only one dose was tested, age/health of study animals were not reported, and a mode of action/adverse outcome pathway was not established.

The EPA has been collaborating with the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences to develop research intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity. The results of this research will be considered when available. Additional information on the NTP research plan for glyphosate is available online: <https://ntp.niehs.nih.gov/results/areas/glyphosate/index.html>.

If at any time, information becomes available that indicates adverse human health effects of concern for exposure to glyphosate or its formulations, the EPA intends to review it and determine the appropriate regulatory action.

Comments About the Monarch Butterfly:

Many commenters such as the Center for Food Safety, Center for Biological Diversity, Natural Resource Defense Council, and Beyond Pesticides expressed concerns that the EPA's risk assessment is not protective of monarch butterflies and plant resources for monarchs, such as milkweed. In general, commenters asserted that the EPA has not done enough to protect monarch butterflies when monarch populations have been in decline in recent decades. Commenters urged the EPA to restrict or ban glyphosate on the grounds that it is killing milkweed, a key resource for monarch butterfly larvae.

The EPA Response: Monarch butterfly conservation is an important issue for the agency. While herbicides like glyphosate have been implicated in the decline of the monarch butterfly population, it is not known to what extent pesticides in general may play a role. It is important to note that threats to the monarch butterfly population are multi-pronged and include loss of breeding habitat, loss of overwintering habitat in Mexico,² changes in weather patterns (including winter storms), disease, and other factors.³

² Vidal, O., Lopez-Garcia, J., and Rendon-Salinas, E. (2014), Trends in Deforestation and Forest Degradation after a Decade of Monitoring in the Monarch Butterfly Biosphere Reserve in Mexico. *Conservation Biology*, 28: 177-186.

³ Agrawal, A. and Inamine, H. (2018), Mechanisms behind the monarch's decline. *Science*, 22: vol. 360, Issue 6395, pp.1294-1296.

A holistic approach is needed for monarch conservation and such an approach should consider herbicides in general as well as other factors that may play a role in the monarch decline. In addition, it is important to balance weed management needs with monarch conservation needs. To that end, the EPA published the *Risk Management Approach to Identifying Options for Protecting the Monarch Butterfly* for public comment in 2015 (available in docket EPA-HQ-OPP-2015-0389 at www.regulations.gov). In this document, the EPA sought feedback from stakeholders on strategies for managing risks to monarch butterflies and sought specific information on factors affecting the monarch population, including information such as:

- i. volume of use of various herbicides in areas critical to the monarch butterfly and where milkweed species are commonly found;
- ii. information on the monarch butterfly lifecycle, seasonal distribution, its population demographics over time, and any modeling analysis relevant to critical life stage parameters;
- iii. availability of laboratory or field data that specifically relates to the effects of various herbicides on the milkweed plant species;
- iv. information on both spatial and temporal parameters of weed management needs particularly where herbicide use may overlap with habitat of the monarch butterfly development, reproduction, and migration; and
- v. information on existing practices that promote co-occurrence of agricultural production with maintenance of milkweed populations.

Overall, the EPA received good suggestions from stakeholders on how to manage risks to monarch butterflies. Suggestions from stakeholders include the following:

- i. broad stakeholder involvement, outreach, and partnering;
- ii. focusing on voluntary, incentive-based, and locally-led initiatives;
- iii. promotion and use of best management practices to reduce pesticide exposure;
- iv. promotion and use of integrated pest management;
- v. development of label language to protect the monarch butterfly;
- vi. supporting milkweed habitat in non-agricultural areas;
- vii. more communication, education, and outreach on the monarch butterfly;
- viii. continue to better understand monarch biology and needs; and
- ix. ensure that any actions taken are done in a manner that balances monarch conservation priorities with other priorities such as native and invasive weed control.

In general, the EPA has focused its monarch conservation efforts on activities that are within the purview of the Office of Pesticide Programs (OPP) and are possible to implement through OPP's registration review, registration, and stakeholder outreach activities. The EPA is focused on four main areas: label language; cooperative efforts between the EPA and other federal, state, and private partners/stakeholders; outreach and communication; promoting best management practices and integrated pest management; and science and risk assessment. In the last several years, the EPA has made progress in many of these focus areas. Major milestones achieved include the following:

- In 2017, the EPA promoted pollinator/monarch conservation activities at the state level by finalizing the *2018-2021 FIFRA Cooperative Agreement Guidance*⁴ for states. The

⁴ <https://www.epa.gov/compliance/fiscal-year-2018-2021-fifra-cooperative-agreement-guidance>

2018-2021 Cooperative Agreement Guidance was modified to include the following monarch conservation activities:

- Establish/maintain relationships with federal, state, tribal and local agencies, beekeeper organizations, grower organizations (e.g., commodity groups), crop advisors, pesticide manufacturers (registrants), and other stakeholder groups within the region to assist where needed in combined pollinator protection activities.
- Providing continuing education opportunities to keep growers, applicators, and handlers up-to-date on the most recent methods to protect pollinators (including monarchs), such as integrated pest management, best management practices, and integrated vegetation management.
- Developing and implementing managed pollinator protection plans focusing on managed bees, as well as monarch butterflies and other native pollinators.
- Work with co-regulators and stakeholders to develop measures to determine the effectiveness of these plans in reducing pesticide risk to pollinators.
- Provide technical assistance, education and outreach to support habitat restoration efforts to enhance/supplement forage for bees and other pollinators, such as the monarch butterfly.
- Promote the use of best management practices, integrated roadside vegetation management, and mowing best practices in roadsides, rights-of-ways, or managed natural areas which may support pollinator habitat and in turn support foraging honeybees, monarch butterflies, and other pollinators.

EPA regulates the registration, distribution, sale, and use of pesticides. The states have primary authority for pesticide compliance monitoring and enforcement. EPA provides funds to the states for pesticide education and outreach as well as compliance monitoring and enforcement activities under the FIFRA State and Tribal Continuing Environmental Program cooperative agreements⁴. FIFRA Cooperative Agreement Guidances, which are periodically updated, outline areas of cooperation between the EPA and the states and tribes, and describe specific pesticide program activities where grant money may be disbursed. Adding monarch conservation activities to the 2018-2021 FIFRA Cooperative Agreement Guidance empowers states to prioritize pollinator/monarch conservation activities depending on each state's needs and priorities.

- In 2017, the EPA adopted advisory environmental hazards label language for pesticide products that are toxic to plants in its Interim Registration Review Decisions to alert pesticide users of potential effects to non-target organisms: *"This product is toxic to plants and may adversely impact the forage and habitat of non-target organisms, including pollinators, in areas adjacent to the treated area. Protect the forage and habitat of non-target organisms by minimizing spray drift. For further guidance and instructions on how to minimize spray drift, refer to the Spray Drift Management section of this label."*
- In 2018, the EPA organized four webinars to educate stakeholders on ways to reduce pesticide spray drift and ways to use integrated pest management principles in managing agricultural lands. The webinars are as follows:

- *Strategies for Managing Pesticide Spray Drift Webinar*, covered the fundamentals of spray drift management.⁵
 - *Integrated Pest Management: Strategies for Pollinator Habitat Promotion and Conservation in Agricultural Areas*, covered integrated pest management principles for managing agricultural lands.⁶
 - *Best Practices for Aerial Application*, a more in-depth look at aerial application.⁶
 - *Best Practices for Ground Application*, a more in-depth look at ground application.⁶
- The EPA is continuing to collaborate with states, federal agencies, and other stakeholders in order to coordinate on conservation efforts and aid in scientific risk assessment. For example, the EPA is currently working with the Fish and Wildlife Service on [the assessment of the monarch butterfly species status](#), and is engaged in discussions with the US Department of Agriculture, the State FIFRA Issues Research And Evaluation Group ([SFIREG](#)), and the Association of American Pesticide Control Officials ([AAPCO](#)) on various pesticide policy issues, including pollinator/monarch protection efforts.

Stakeholders are encouraged to visit the EPA's new monarch butterfly website for resources and news on the monarch front: <https://www.epa.gov/pollinator-protection/protecting-monarch-butterflies-pesticides>. In this proposed interim registration review decision for glyphosate, the agency is proposing risk mitigation measures to manage off-target spray drift to protect non-target organisms. Further information on the EPA's proposed interim decision and the agency's rationale is described in Section IV of this document.

Comments About Pollinators:

Several commenters, including the Pollinator Stewardship Council and Colorado State Beekeepers Association, discussed potential direct effects to honey bees and their health, particularly as it related to sublethal effects on honey bee navigation and appetite and cited various open literature references about honey bee health.

The EPA Response: The agency appreciates this additional information concerning honey bee toxicity data. There is uncertainty regarding the relationship of sublethal effects such as inhibition of navigation and loss of appetite, relative to the EPA's standard assessment endpoints (*i.e.*, impaired survival; growth; development). Additionally, the ecological assessment included discussion about a study that tested for colony-level effects (Thompson et al, 2014), which did not show that glyphosate adversely affected adult or developing young (brood). The EPA may require additional pollinator data in order to complete its evaluation of risk to bees prior to a final decision for registration review.

⁵ This webinar's materials are posted online at: <https://www.epa.gov/reducing-pesticide-drift/strategies-managing-pesticide-spray-drift-webinar-materials>

⁶ EPA is working on posting the materials for this webinar.

Comments on the Presence of Glyphosate in Surface Water:

Several commenters such as Beyond Pesticides and Friends of the Earth cited a recent report from the US Geological Survey (USGS) indicating that glyphosate had been detected in aquatic systems.

The EPA Response: The agency is aware of the recent 2014 USGS report (https://toxics.usgs.gov/highlights/2014-04-23-glyphosate_2014.html). The USGS monitoring data were considered as part of the EPA's ecological risk assessment (see Section 3.4 of the ecological risk assessment). The USGS data are ambient monitoring data and not targeted spatially or temporally to glyphosate use, so the extent that monitoring detections directly correlate to certain glyphosate applications is uncertain. These data have limited use for risk calculation but are useful as an additional line of evidence. The occurrence of glyphosate in some waterbodies (aside from its uses that include direct applications to certain waterbodies) is consistent with the EPA's analysis and was factored into risk assessment.

Comments Relating to Endangered Species Risk Assessment and Synergy:

The Center for Biological Diversity (CBD) submitted comments which focus on the EPA's duty to consult with the Services on the registration review of glyphosate in accordance with the Endangered Species Act (ESA). The CBD's comments mention various aspects of the risk assessment process, specifically use of the best available data, including all necessary data and studies, particularly to develop listed species risk assessments, and evaluation of effects on listed species and their designated critical habitat. CBD also expressed concern regarding the rigor of the agency's preliminary determinations regarding the effects of glyphosate on listed species and their designated critical habitat for the glyphosate registration review. In addition, CBD expressed concern about effects on pollinators and other beneficial insects, effects on human health or environmental safety concerning endocrine disruption, and any additive, cumulative or synergistic effects of the use of the pesticide.

The EPA Response: The EPA plans to address many of the concerns regarding listed species as part of the implementation plan for assessing the risks of pesticides to listed species based on the recommendations of the April 2013 National Academy of Sciences (NAS) report. See Endangered Species Assessment in Appendix D of this document for more information. The EPA will address concerns specific to glyphosate particularly with regard to pollinators, ESA, and endocrine disruption, in connection with the development of its final registration review decision for this pesticide. See Endocrine Disruptor Screening Program in Appendix E of this document for more information regarding endocrine disruption. The EPA is currently developing an agency policy on how to consider claims of synergy being made by registrants in their patents. The EPA intends to release this policy for public comment. After the agency has received and considered public comment on the proposed policy, and once that policy has been finalized, the EPA will consider its implications on the EPA's registration review decision for glyphosate.

Comments Relating to the EPA's Use Reports for Glyphosate:

A number of private citizens expressed concern that the EPA did not adequately assess the large volume of glyphosate use and the large number of use sites as part of registration review. Some commenters, such as Center for Food Safety, requested that the EPA update its use reports for glyphosate and provide more accurate estimates of use and usage.

The EPA Response: At various points in registration review, the EPA has provided estimates of agricultural usage for glyphosate. The following use reports were previously published in the glyphosate registration review docket: the 2008 *Screening Level Estimates of Agricultural Uses of the Case Glyphosate* and the 2015 *Updated Screening Level Usage Analysis (SLUA) Report for Glyphosate Case PC #s (103601, 103604, 103607, 103608, 103613, 417300)*. As part of this proposed interim registration review decision, the EPA is also providing updated agricultural and non-agricultural usage information, which are included in the *Glyphosate: Response to Comments, Usage, and Benefits*, also available in the public docket. A summary of all the current use sites for glyphosate along with current labeled applications rates and other application parameters are also available in the *Joint Glyphosate Task Force's Use Summary Matrix*, available in the glyphosate public docket.

Comments on Glyphosate's Connection to Resistant Weeds:

Many stakeholders (*e.g.*, Beyond Pesticides, Center for Food Safety, Center for Biological Diversity) commented on glyphosate's connection to weed resistance, stating that widespread use of glyphosate has resulted in increased weed resistance, particularly in glyphosate-resistant crops. Commenters noted that there is potential for resistance to spread between herbicide resistant crops and related plants. Other stakeholders (*e.g.*, Kansas Agribusiness Retailers Association, Almond Alliance of California, Iowa Corn Growers Association) state that glyphosate is effective on weeds that are resistant to other herbicides and is still a useful tool for growers despite weed resistance issues.

The EPA Response: Whenever a herbicide is used, there is a potential for that use to contribute to the evolution of herbicide resistance, particularly if the population of a weed species is subjected to repeated sublethal doses of herbicide. Weed resistance commonly occurs but despite resistance problems, glyphosate remains an important weed management tool. Glyphosate is still effective on many weed species that have shown resistance to other herbicides. To combat weed resistance, EPA encourages tank-mixing herbicides, rotating different mechanisms of action, crop rotation, and the use of integrated pest management programs. To maintain some of the most important benefits of glyphosate, growers must use herbicides responsibly as part of an integrated weed control strategy and be proactive in employing good weed resistance management practices.

Herbicide resistance can occur through pollen-mediated gene flow from resistant crops to weedy relatives. Additionally, glyphosate-resistant biotypes of some weeds can rapidly disperse through pollen-mediated gene flow. The United States Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) regulates the planting, importation, or transportation of genetically engineered plant crops under the Plant Protection Act. Most genetically engineered plants are "regulated articles" and must receive prior approval from APHIS before introduction.

Helping to educate growers on how to manage weed resistance is a top priority for the agency. The EPA is proposing to require herbicide resistance management labeling as part of this Proposed Interim Registration Review Decision (see section IV of this document). The EPA has also published two Pesticide Registration Notices (PRNs) which address pest resistance management. PRN 2017-1⁷ promotes mechanism of action labeling by pesticide registrants. PRN 2017-2⁸ provides specific guidance for managing herbicide resistance, including labeling, education, training, and stewardship strategies for pesticide manufacturers, producers, formulators, states, grower groups, growers, and other interested stakeholders.

Comments from Mass Mail Campaigns:

The EPA received comments from nine mass mail campaigns. Two mass mail campaigns were organized by Bayer Crop Science and an unidentified organization and included comments from farmers, agricultural professionals, and general consumers urging the EPA to keep glyphosate accessible. Seven mass mail campaigns came from the following environmental non-governmental organizations: Friends of the Earth, Center for Food Safety, Environmental Action, Pesticide Action Network, Organics Consumer Association, Center for Biological Diversity, and an unidentified organization. These seven campaigns urged the EPA to restrict glyphosate, protect the monarch butterfly, and/or reconsider its cancer conclusion.

The EPA Response: The agency has conducted comprehensive human health and ecological risk assessments for glyphosate and has not received any information from public comments that would warrant revising the conclusions of its risk assessments. The EPA did not identify any risks of concern for humans from exposure to glyphosate. In addition, the agency determined glyphosate is not likely to be carcinogenic to humans. The EPA has identified risks primarily from spray drift for non-target organisms. The agency has weighed the risks and benefits of glyphosate use as part of its proposed interim registration review decision. In general, the benefits that glyphosate confers to growers outweighs the geographically limited risks to non-target organisms. It is important to balance the needs of weed management with protections for non-target organisms and the agency is proposing risk mitigation measures to manage off-target spray drift and promote weed resistance management. Further information on the EPA's proposed interim decision and the agency's rationale is described in Section IV of this document.

Comments from USDA's Office of Pest Management Policy:

In its comments to the glyphosate registration review docket, USDA submitted information on the benefits of glyphosate, and furnished information on the non-agricultural uses of glyphosate, particularly in non-food tree crops, aquatic areas, and pasture/natural lands.

The EPA Response: The agency thanks USDA for its comments and especially appreciates the information on use of glyphosate in non-agricultural areas, as that information is not readily

⁷ *Guidance for Pesticide Registrants on Pesticide Resistance Management Labeling*. <https://www.epa.gov/pesticide-registration/prn-2017-1-guidance-pesticide-registrants-pesticide-resistance-management>

⁸ *Guidance for Herbicide-Resistance Management, Labeling, Education, Training, and Stewardship*. <https://www.epa.gov/pesticide-registration/prn-2017-2-guidance-herbicide-resistance-management-labeling-education>

available. The benefits and information on application rate, timing, and typical practices for non-agricultural uses have been considered as part of this Proposed Interim Registration Review Decision.

II. USE AND USAGE

Glyphosate is a broad-spectrum, systemic glycine herbicide which inhibits the enzyme enolpyruvyl shikimate-3-phosphate (EPSP) synthase in plants and inhibits aromatic amino acid synthesis. It is the only herbicide in the Weed Science Society of America's (WSSA) group 9 class and it has a unique mode of action. Glyphosate is formulated as ready-to-use solution, water-dispersible granules, soluble concentrate, emulsifiable concentrate, flowable concentrate, water soluble packaging, pressurized liquid, pellets/tablets, and tree injection shells. It can be applied as a pre-emergent, post-emergent, or as a pre-harvest application to the crop to treat a variety of emerged grass and broadleaf weeds. In a few crops (ex. sugarcane), glyphosate is used as a plant growth regulator.

Glyphosate is registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, legumes, cereal grains, and other field crops. Glyphosate is also registered for use on glyphosate-resistant (transgenic) crops such as corn, soybean, cotton, canola, sugar beets, and alfalfa. Registered non-agricultural uses include: tree injections, residential spot treatments, aquatic areas, forests, rights of ways, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land.

Application methods vary for glyphosate and include aircraft, various ground equipment, and various handheld equipment. Application types include: aerial spray, ground boom spray, strip treatment, band treatment, broadcast spray, spot treatment, tree injection, stump treatment, and wipe-on/wiper treatments. The maximum single application rate on labels is up to 8 pounds acid equivalent per acre (lb ae/A) (acid equivalents or ae are used to assess the different acid and salt forms of glyphosate) for the following uses: pastures, non-food tree crops, forestry, aquatic areas, and non-crop. However, for agricultural row crop uses, maximum single application rates are 1.55 lb ae/A for aerial applications and 3.75 lb ae/A for ground applications. Maximum annual application rates are generally 6 to 8 lbs ae/A.

The EPA completed a new usage analysis for glyphosate by analyzing agricultural market research data from 2012 to 2016. Approximately 281 million pounds of glyphosate was applied to 298 million acres annually in agricultural settings. Most glyphosate was applied to soybean (approximately 117.4 million lbs applied annually), corn (approximately 94.9 million lbs applied annually), and cotton (approximately 20 million lbs applied annually). Many citrus fruits (e.g., grapefruit, oranges, lemons), field crops (e.g., soybean, corn, cotton), and tree nuts (e.g., almonds, walnuts, pistachios) have the highest percentage of their acres treated with glyphosate.

Approximately 24 million pounds of glyphosate are applied to non-agricultural sites annually, on average. The majority of non-agricultural use is for the homeowner market (approximately 5 million lbs applied annually), turf (approximately 4.9 million lbs applied annually), forestry

(approximately 3.6 million lbs applied annually), and roadways (approximately 3.3 million lbs applied annually).

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

A summary of the agency's human health risk assessment is presented below. The agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of glyphosate. For additional details on the human health assessment for glyphosate, see the *Glyphosate Draft Human Health Risk Assessment for Registration Review*, which is available in the public docket.

1. Risk Summary

The EPA thoroughly assessed risks to humans from exposure to glyphosate from all uses and all routes of exposure and did not identify any risks of concern. Both non-cancer and cancer effects were evaluated for glyphosate and its metabolites, aminomethyl phosphonic acid (AMPA) and N-acetyl-glyphosate. The different components of the EPA's human health risk assessment are described below.

Cancer Assessment

The EPA convened a FIFRA SAP meeting in December 2016 to consult on the carcinogenic potential of glyphosate. Recommendations from the Scientific Advisory Panel meeting were published in March 2017. The EPA revised its cancer assessment based on comments received from the SAP and responded to the SAP in the *Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate*. The EPA's final cancer conclusion and its rationale for reaching this conclusion is described in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*. The EPA's final cancer assessment includes the newly published analysis of glyphosate use and cancer incidence in the Agricultural Health Study (AHS). The AHS study is a long-term epidemiological study of over 54 thousand pesticide applicators to investigate the association between pesticide exposures and incidence of various types of cancer and non-cancer outcomes. The EPA's review of the AHS study is described in the *Summary Review of Recent Analysis of Glyphosate Use and Cancer Incidence in the Agricultural Health Study*. The agency has determined that glyphosate is not likely to be carcinogenic to humans and therefore a quantitative cancer assessment was not conducted.

All documents relating to the cancer evaluation for glyphosate are published in the public registration review docket for glyphosate (EPA-HQ-OPP-2009-0361). The deliberations of the glyphosate FIFRA SAP meeting, including agenda, meeting notes, SAP recommendations, the EPA's presentation to the FIFRA SAP, and other supporting documents are published in the glyphosate FIFRA SAP docket (EPA-HQ-OPP-2016-0385) at www.regulations.gov.

The Agency has received a September 27, 2018 petition from the Environmental Working Group, Ben & Jerry's Homemade, Inc., Happy Family Organics, MegaFood, MOM's Organic Market, National Co-op Grocers, Nature's Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farms, Inc. requesting that the agency reduce the tolerance of the pesticide glyphosate in or on oats and modify labels to explicitly prohibit preharvest use on oats. The agency is still reviewing this petition and has issued a Federal Register Notice of Filing for public comment in docket EPA-HQ-OPP-2019-0066. The petition references EPA's cancer evaluation and includes the following arguments:

- 1) EPA's tolerance for oats is not adequately protective of children, due to the widespread use of glyphosate and a lack of glyphosate residue monitoring data. The petitioners submit results of residue testing from the EWG of glyphosate levels in various granola, instant oat, breakfast cereal, and snack commodities as evidence of this assertion.
- 2) Glyphosate is a possible carcinogen according to the International Agency for Research on Cancer (IARC), who classified glyphosate as "probably carcinogenic to humans" in 2015.
- 3) Human studies demonstrate a likely link between glyphosate exposure and non-Hodgkin lymphoma.
- 4) Animal models, when viewed in total, suggest glyphosate is a rodent carcinogen.
- 5) Analyses of glyphosate animal studies by the European Food Safety Authority and the European Chemicals Agency were flawed, and the incidence of tumors is higher than reported.
- 6) Petitioners point to comments sent from the Office of Research and Development, which were sent to the Office of Pesticide Programs (OPP) while the agency's cancer evaluation was being drafted in 2015, as a line of evidence, contending that OPP should have been more circumspect about rejecting IARC's cancer conclusion.
- 7) EWG calculated its own cancer risk level and proposed that the level protective of children's health is 0.01 milligrams of glyphosate per day. The petitioners contend that EPA's dietary risk assessment is not adequately protective of children.

Since this petition was submitted outside of the public comment period for the human health and ecological risk assessments, which closed on April 30, 2018, EPA has not considered it as a public comment in the preparation this Proposed Interim Registration Review Decision. EPA will respond to this petition concurrent with the development of its Interim Registration Review Decision for glyphosate. The risk findings described herein reflect the conclusions of EPA's December 12, 2017 human health risk assessment.

Dietary (Food + Water) Risks

An acute dietary assessment was not completed because an acute reference dose could not be established due to the absence of observable adverse effects seen in acute studies. A cancer dietary assessment was not conducted because glyphosate is classified as not likely to be carcinogenic to humans.

Long-term toxicity studies in mice, rats, and dogs demonstrate that glyphosate is of very low toxicity following repeated oral exposure. Rabbits were the most sensitive species tested and the endpoint chosen for chronic dietary assessment was based on diarrhea and few/no feces. A

conservative chronic dietary risk assessment was conducted assuming tolerance-level residues, modeled drinking water estimates from direct application to water scenarios, 100% crop treated assumptions, and default modeling parameters. The resulting chronic dietary risk estimates were not of concern. Children 1-2 years old were the most highly exposed population subgroup (chronic population adjusted dose [cPAD] = 23%, where a cPAD above 100% exceeds the agency's level of concern).

Breast Milk Analysis

In response to concerns from certain segments of the public related to the potential presence of glyphosate in human breast milk, the EPA analyzed human breast milk samples collected by the National Children's Study for residues of glyphosate and glyphosate metabolites (N-acetyl-glyphosate and AMPA). A total of 39 samples from 39 mothers were analyzed. Glyphosate and its metabolites were not detected in human breast milk samples. For additional details on the EPA's breast milk analysis and methodology, please view the following documents in the glyphosate registration review docket:

- *Analysis of Human Milk for Incurred Residues of Glyphosate and its Metabolites. ACB Project #B14-46—Updated from Report Dated September 18, 2015* (dated April 26, 2016)
- *Analytical Method for the Determination of N-Acetylglyphosate and Other Analytes in Various Animal Matrices Using LC/MS/MS* (undated)

The results of the EPA's breast milk analysis is consistent with the scientific literature for glyphosate, which indicates that glyphosate does not bioaccumulate in the human body.

Residential Handler Risks

The EPA considered the potential for short-term dermal and inhalation exposures to homeowners who mix and apply products containing glyphosate (residential handlers). A quantitative residential handler assessment was not completed due to lack of toxicity from short- and intermediate-term dermal and inhalation routes of exposure. Residential handler risks are not anticipated from currently registered uses of glyphosate.

Residential Post-Application Risks

Post-application dermal and inhalation assessments were not quantitatively assessed due to lack of toxicity. However, a short- and intermediate-term post-application incidental oral exposure assessment was conducted to assess potential risk from two scenarios: 1) for hand-to-mouth behavior on treated lawns and 2) for swimmers via short-term post-application incidental oral exposure to glyphosate from the aquatic use. Post-application incidental oral risk estimates for the turf use were not of concern, with Margins of Exposure (MOEs) ranging from 640 to 290,000, where MOEs below 100 are of concern. Post-application swimmer risk estimates for the aquatic use were not of concern (MOEs range from 210,000 to 2,200,000, where MOEs below 100 are of concern). Therefore, residential post-application risks are not anticipated from currently registered uses of glyphosate.

Non-Occupational Bystander Spray Drift Risks

The EPA assessed the potential for risk to non-occupational bystanders from off-target movement of glyphosate via spray drift, to protect from indirect exposure (*e.g.*, children playing on lawns where residues have deposited next to treated fields). Since glyphosate is registered for use on turf, it was considered whether the existing turf post-application assessment was protective of bystander exposure via spray drift. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. The currently registered maximum single agricultural application rate for glyphosate is 8 lbs ae/A (for use on pastures, forestry, non-food tree crops, etc.). The highest fraction of spray drift for any application method immediately adjacent to a treated field results in a deposition fraction of 0.26 of the application rate (from AgDrift modeling). The maximum application rate adjusted by the 0.26 adjustment factor for drift ($8 \text{ lb ae/A} \times 0.26 \text{ lb ae/A} = 2.08 \text{ lb ae/A}$) is less than the assessed maximum direct spray residential turf application rate (10.5 lb ae/A). Therefore, the turf post-application assessment is protective for any potential bystander spray drift exposure, and a quantitative spray drift assessment for glyphosate was not required. Therefore, non-occupational bystander spray drift risks are not of concern for glyphosate.

Aggregate Risks

Aggregate risk assessment considers exposure from food, drinking water, and residential exposures combined. The EPA conducted short-term (food, water, residential) and chronic (food and water) aggregate risk assessments. Acute and cancer aggregate risk assessments were not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup and glyphosate is classified as not likely to be carcinogenic to humans, respectively. An intermediate-term assessment was not conducted since the short-term assessment is protective of intermediate-term exposure (the endpoints for these durations are identical). Short-term aggregate risks were not of concern (MOE for children = 260, MOE for adults = 1,300, where MOEs below 100 are of concern). The MOE for children represents exposure from chronic dietary (food and water) and incidental oral ingestion exposure from turf use, which was the highest exposure scenario. The MOE for adults represents chronic dietary exposure (food and water) and incidental oral ingestion exposure resulting from aquatic use, the highest exposure scenario.

Chronic aggregate risks were also not of concern. Chronic aggregate exposure is from dietary (food and water) exposure only, based on the use pattern, and are the same as the chronic dietary risk estimates ($\leq 23\%$ cPAD, see dietary section).

Cumulative Risks

The EPA has not made a common mechanism of toxicity to humans finding as to glyphosate and any other substance and it does not appear to produce a toxic metabolite produced by other substances. Therefore, the EPA did not assess cumulative risks for this assessment.

Occupational Risks

A quantitative occupational exposure assessment was not conducted due to lack of toxicity via the occupational handler and post-application dermal and inhalation routes of exposure. Therefore, occupational risks from currently registered uses of glyphosate are not of concern.

The current restricted entry interval (REI) on the labels is 12 hours or 4 hours, depending on the glyphosate formulation. The current human health risk assessment supports a 4 hour REI for glyphosate the active ingredient, but the different glyphosate formulations were not assessed. According to *PRN 95-3: Reduction of Worker Protection Standard (WPS) Interim Restricted Entry Intervals (REIs) for Certain Low Risk Pesticides*, certain glyphosate formulations may qualify for a reduced 4 hour REI. Glyphosate registrants may use the existing label amendment process to request a reduction in the existing 12 hour REI to a 4 hour REI on the label, on a formulation by formulation basis.

2. Human Incidents and Epidemiological Analysis

The EPA conducted an extended incident search for glyphosate human health incidents in February 2014. Five pesticide incident data sources were reviewed: Office of Pesticide Programs Incident Data System (IDS; 2008-2012), National Pesticide Information Center (NPIC; 2007-2013), California's Pesticide Incident Surveillance Program (PISP; 2005-2010), National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH/SENSOR; 1998-2009), and the American Association of Poison Control Centers (AAPCC; 2001-2012). Thousands of glyphosate incidents were reported but most reported incidents were minor in severity. The high number of reported incidents across the databases is likely a result of glyphosate being among the most widely used pesticides by volume. Health effects reported in the incident databases include dermal, ocular, and respiratory symptoms and effects are generally mild and resolve rapidly. Data from IDS and NPIC suggest that homeowner mixing/loading/applying (usually due to human error and container leaks of glyphosate products) are responsible for almost half of reported incidents. Data from SENSOR-Pesticides are consistent with IDS and NPIC and show that glyphosate application results in the most reported incidents. Occupational handling of equipment is responsible for most incidents in California's PISP database due to equipment leaks and malfunction. Across SENSOR, IDS, and NPIC, children's exposure was due to post-application exposure, accidental ingestion, and tampering with the product.

The medical-case literature was reviewed, and most accidental ingestion of glyphosate formulations result in mild symptoms. Intentional ingestions caused moderate to severe symptoms and involved multiple organ systems.

The epidemiological literature was also reviewed but most studies were hypothesis-generating in nature. The EPA found there was insufficient evidence to conclude that glyphosate plays a role in any human diseases. The agency will continue to monitor the incident information. Additional analyses will be conducted if ongoing human incident monitoring indicates a concern.

An updated incident search was conducted in the IDS on October 26, 2018 for new human health incidents. From January 1, 2014 to October 25, 2018, 249 incidents were reported in the Main IDS involving glyphosate. Of these, there were 3 deaths, 24 incidents were classified as major

severity, 216 incidents were classified as moderate severity, 5 incidents were classified as minor severity, and 1 incident had no or unknown effects. Of the three reported deaths, two were suicides and one was described as a “Roundup overdose.” From January 1, 2014 to October 25, 2018, 3,123 incidents were reported to Aggregate IDS involving glyphosate; most were classified as minor severity and the rest had no effects or unknown effects.

For more information on reported human incidents, see the *Glyphosate: Tier II Incident Report*, available in the in the public docket for glyphosate.

3. Tolerances

Tolerances are established for residues of glyphosate in/on numerous plant commodities in 40 CFR § 180.364. Glyphosate tolerances range from 0.2 to 400 ppm. The EPA evaluated the glyphosate residue chemistry database to determine if the established tolerances conform to current practices and to determine whether updates were necessary for current crop group/subgroup definitions. The EPA intends to establish new tolerances for various vegetable and fruit groups and subgroups, as listed in Table 1. Upon establishment of these new crop group tolerances, EPA intends to remove the following individual tolerances, since they will no longer be needed: acerola; aloe vera; ambarella; asparagus; atemoya; avocado; bamboo, shoots; banana; biriba; breadfruit; cactus, fruit; cactus, pads; canistel; cherimoya; custard apple; date, dried fruit; durian; feijoa; fig; fruit, stone, group 12; guava; ilama; imbe; imbu; jaboticaba; jackfruit; longan; lychee; mamey apple; mango; mangosteen; marmaladebox; noni; nut, tree, group 14; olive; palm heart; papaya; papaya, mountain; passionfruit; pawpaw; persimmon; pineapple; pistachio; pomegranate; pulasan; rambutan; rose apple; sapodilla; sapote, black; sapote, mamey; sapote, white; soursop; Spanish lime; star apple; starfruit; sugar apple; Surinam cherry; tamarind; vegetable, leafy, brassica, group 5; vegetable, leafy, except brassica, group 4; watercress, upland; and wax jambu.

Table 1. Proposed Changes to the Tolerance Levels or Commodity Definitions for Glyphosate.

Current		Proposed Change		Comment
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)	
Soybean, forage	100.0	Soybean, forage	100	change in number of significant figures
Soybean, hay	200.0	Soybean, hay	200	
Soybean, hulls	120.0	Soybean, hulls	120	
Soybean, seed	20.0	Soybean, seed	20	
Fruit, stone, group 12	0.2	Fruit, stone, group 12-12	0.2	update to the current crop group definitions; coconut was excluded from the tree nut crop group tolerances as the residues were not within 5x (coconut tolerance at 0.1 ppm)
Nut, tree, group 14	1.0	Nut, tree, group 14-12 (except coconut)	1.0	
Vegetable, leafy, except brassica, group 4	0.2	Vegetable, leafy, group 4-16	0.2	update to the current crop group definitions
Vegetable, leafy, brassica, group 5	0.2	Vegetable, <i>Brassica</i> , head and stem, group 5-16	0.2	

Table 1. Proposed Changes to the Tolerance Levels or Commodity Definitions for Glyphosate.				
Current		Proposed Change		Comment
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)	
Several	0.2-0.5--	Vegetable, stalk and stem, subgroup 22A	0.5	
	0.2	Vegetable, leaf petiole, subgroup 22B	0.2	
	0.2	Fruit, tropical and subtropical, edible peel, group 23	0.2	
	0.2	Fruit, tropical and subtropical, small fruit, inedible peel, group 24A	0.2	
	0.2	Fruit, tropical and subtropical, medium to large fruit, smooth, inedible peel, group 24B	0.2	
	0.2	Fruit, tropical and subtropical, large fruit, rough or hairy, inedible peel, group 24C	0.2	
	0.2	Fruit, tropical and subtropical, vine, inedible peel, group 24E	0.2	

In accordance with FFDCA, the Agency will be conducting rulemaking to implement any tolerance changes identified for glyphosate.

4. Human Health Data Needs

No human health data needs have been identified for glyphosate. The human health data required as part of the registration review DCI has been satisfied.

B. Ecological Risks

A summary of the agency's ecological risk assessment is presented below. The agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of glyphosate. For additional details on the ecological assessment for glyphosate, see the *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*, which is available in the public docket.

The EPA is currently working with its federal partners and other stakeholders to implement an interim approach for assessing potential risk to listed species and their designated critical habitats. Once the scientific methods necessary to complete risk assessments for listed species and their designated critical habitats are finalized, the agency will complete its endangered species assessment for glyphosate. See Appendix D for more details. As such, potential risks for non-listed species only are described below. See section III.C of this document for additional risk characterization.

1. Risk Summary

Terrestrial Risks

To assess risk to mammals, birds, terrestrial invertebrates, and terrestrial plants, the EPA reviewed both registrant-submitted studies and studies from the open literature. When available, formulation-specific data were also considered in addition to data on glyphosate alone.

Mammals

Acute risks to mammals are expected to be low for technical grade glyphosate. Acute risk quotients (RQs) were not calculated for mammals because the lethal dose sufficient to kill 50% of a population (LD₅₀) is greater than the highest concentrations tested (up to 4,800 milligrams acid equivalent per kilogram of bodyweight [mg ae/kg-bw]) in the available acute oral toxicity study. Estimated Environmental Concentrations (EECs) for all uses except spot treatment are below the highest concentration tested in the available acute oral and acute dietary studies. However, the application rate for spot treatments is adjusted to a per acre basis and conservatively assumes that the entire area is treated at that high rate.

In addition to toxicity studies with technical grade glyphosate, acute dose-based toxicity studies were available for various formulations. RQs exceeded the level of concern (LOC) of 0.5 for one formulation (11.4% glyphosate; acute RQs ≤ 2.1) for labeled use on broadcast brush at a rate of 7.2 lb ae/A. Data for most formulations showed LD₅₀ values greater than the highest dose tested.

Chronic dietary-based RQs for technical grade glyphosate did not exceed the LOC for any use patterns, except spot treatment (RQs ≤ 1.92 , where the LOC=1). However, chronic dose-based RQs did exceed the LOC for the following scenarios:

- i. application to sugarcane at rates of 2.25 lb ae/A and above (RQ=1.02),
- ii. application to most conventional crops by ground at rates of 3.75 lb ae/A and above (RQ ≤ 1.21),
- iii. application to Roundup-ready crops at the maximum annual rate of 6 lb ae/A (RQs ≤ 1.11),
- iv. application to tree crops at a rate of 8 lb ae/A (RQs ≤ 1.03),
- v. application to food trees and vine, berry, and small fruits at the maximum annual rate of 8 lb ae/A (RQs ≤ 1.60),
- vi. application to forestry, pastures, non-crops areas at a rate of 8 lb ae/A (RQs ≤ 2.04),
- vii. application as spot treatments assuming a rate of 40 lb ae/A (RQs ≤ 10.2).

Most chronic dose-based risk exceedances are slightly above the LOC, except for residential spot treatments. The application rate for spot treatment conservatively assumes that the entire acre is treated at a high rate of 40 lb ae/A. Potential risk to mammals from spot treatment use should be limited to residential areas and limited in area.

Birds, Reptiles, and Terrestrial-Phase Amphibians

Potential acute risks to birds from exposure to technical grade glyphosate are likely to be nearer to the level of concern at application rates lower than 8 lb ae/A. There were no mortalities in any of the acute oral or acute dietary avian studies with technical glyphosate (LD₅₀ values $>3,196.3$ mg ae/kg-bw and $>4,971$ mg ae/kg-diet, respectively). Since definitive LD or LC₅₀ values were not determined, RQs were not calculated. EECs for all uses except spot treatment are below the highest concentration tested in the available acute oral and acute dietary studies. However, the application rate for spot treatments is adjusted to a per acre basis and conservatively assumes that the entire area is treated at that high rate.

Regarding the acute toxicity of glyphosate formulations, RQs exceeded the LOC of 0.5 for one formulation (68.5% glyphosate monoammonium salt; acute RQs ≤ 1.26 , based on an LD₅₀ value of 1,131 mg ae/kg-bw for bobwhite quail). Acute avian studies were available for the degradate AMPA and data show it is no more toxic than the parent glyphosate.

Chronic avian RQs were not calculated because the most sensitive endpoint in the avian reproduction study resulted in a non-definitive NOAEC. However, EECs for multiple uses are greater than the lowest concentration tested in the mallard study where effects on body weight were observed (NOAEC <501 mg ae/kg; MRID 48876602). To further characterize the potential for chronic risk from exposure to glyphosate, RQs were calculated using the non-definitive NOAEC from the avian reproduction study with the bobwhite quail where no effects were observed at the highest concentration tested, 830 mg ae/kg-diet. The following scenarios exceed the LOC of 1:

- i. application to most conventional crops at the maximum single aerial rate (1.55 lb ae/A), the maximum single ground rate (3.75 lb ae/A), or above,
- ii. application to Roundup ready crops by ground at the maximum single rate of 3.75 lb ae/A or above,
- iii. application to sugarcane at rates of 2.25 lb ae/A or above,
- iv. application to tree crops at rates of 8 lb ae/A,
- v. application to food trees and vine, berry, and small fruits at 8 lb ae/A, and
- vi. application to forestry, pasture, and non-crop areas at a rate of 8 lb ae/A.

RQs for the scenarios above were marginal (RQs ranged from approximately 1 to ≤ 2.5). Given that there were no reported effects up to the highest concentration tested in the bobwhite quail avian reproduction study, these RQs may be conservative for most uses, but to a lesser extent for use on forests, pastures, and non-crop areas. Application as spot treatment at a rate of 40 lb ae/A resulted in higher risk exceedances, but this scenario was conservatively assessed (RQ ≤ 11.6). Evidence from multiple studies suggest that exposure to glyphosate may result in decreases in body weight, but reproductive parameters such as number of eggs laid, embryo viability, and eggshell thickness may not be impacted.

Terrestrial Invertebrates (honeybees)

Potential risk to terrestrial invertebrates is uncertain, as acute contact and oral honeybee LD₅₀ values are greater than the highest doses tested (103 μg ai/bee for contact, 182 μg ai/bee for oral exposure). Application rates higher than 5.7 lb ae/A exceed the highest tested oral concentrations. Risks to individual bees at application rates lower than 5.7 lb ae/A are expected to be low, but risks are uncertain at rates above 5.7 lb ae/A.

In a colony-level study, no adverse effects were reported based on exposure to residues from an application at a rate of 1.92 lb ae/A.

Data are available for other types of terrestrial invertebrates (predatory mites, earthworms, parasitic wasps) where no effects are reported up to the highest dose tested. The most sensitive endpoint was for predatory mite, and data suggest possible effects up to 69 ft from the edge of

the field for an application rate at 8 lb ae/A, and 16 ft from the edge of the field for an application rate at 3.75 lb ae/A.

Additional data may be necessary to fully evaluate risks to non-target terrestrial invertebrates, especially pollinators. Although the EPA identified the need for certain data to evaluate potential effects on pollinators when initially scoping the registration review for glyphosate, the problem formulation and registration review DCI for glyphosate, were both issued prior to the EPA's issuance of the June 2014 *Guidance for Assessing Pesticide Risks to Bees*⁹. This 2014 guidance lists additional pollinator studies that were not included in the glyphosate registration review DCI. Therefore, the EPA is currently determining whether additional pollinator data are needed for glyphosate. If the agency determines that additional pollinator exposure and effects data are necessary to help make a final registration review decision for glyphosate, then the EPA will issue a DCI to obtain these data. The pollinator studies that could be required for glyphosate are listed in Table 2 below.

Table 2. Potential Pollinator Data Requirements for Glyphosate

Guideline #	Study
Tier 1	
850.3020	Acute contact toxicity study with adult honey bees
850.3030	Honey bee toxicity of residues on foliage
Non-Guideline (OECD 213)	Honey bee adult acute oral toxicity
Non-Guideline (OECD 237)	Honey bee larvae acute oral toxicity
Non-Guideline	Honey bee adult chronic oral toxicity
Non-Guideline	Honey bee larvae chronic oral toxicity
Tier 2 [†]	
Non-Guideline	Field trial of residues in pollen and nectar
Non-Guideline (OECD 75)	Semi-field testing for pollinators
Tier 3 [†]	
850.3040	Full-Field testing for pollinators

[†] The need for higher tier tests for pollinators will be determined based upon the results of lower tiered tests and/or other lines of evidence and the need for a refined pollinator risk assessment.

Terrestrial Plants

Exposure to glyphosate may impact non-target terrestrial plants. Risks from runoff due to glyphosate applications are anticipated to be low. Runoff estimated environmental concentrations were lower than the no observable adverse effect level for plants (based on seedling emergence data).

Potential risks to terrestrial plants are primarily from spray drift. Based on vegetative vigor data, dicots are generally more sensitive to glyphosate than monocots. The most sensitive species tested was cucumber, based on vegetative vigor data for a glyphosate formulation where phytotoxicity was observed (leaf discoloration). A spray drift analysis was completed for both ground and aerial application of glyphosate at various application rates up to 8 lb ae/A, assuming

⁹ http://www2.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf

default droplet size parameters. Fine to medium droplets were assessed for aerial application and very fine to fine droplets were assessed for ground application (based on the American Society of Agricultural and Biological Engineers' [ASABE] droplet size classification standard). Results for the most sensitive species tested, cucumber, are presented in Table 3.

Given its importance as a critical food resource for the monarch butterfly, the agency also completed a spray drift analysis for common milkweed. Reported toxicity endpoints in the literature for common milkweed are similar to the vegetative vigor endpoints for cucumber, the most sensitive species tested (IC₂₅ for cucumber is 0.074 lb ae/A; IC₂₅ for common milkweed is 0.126 lb ae/A). Distances from the edge of the field to be below toxicity threshold (i.e., buffer distances) for both cucumber and milkweed are listed in Table 3.

Table 3. Results of spray drift assessment for terrestrial plants for both aerial and ground application of glyphosate at various application rates

Application rate (lb ae/A), assuming 1 application at each rate	Distance from the edge of the field to be below toxicity threshold for most sensitive species tested (cucumber)	Distance from the edge of the field to be below toxicity threshold for the common milkweed	Spray method
1.55	190	118	Aerial (fine to medium droplets)
2.25	282	171	
3.75	466	279	
8	>1,000	620	
1.55	52	33	Ground (very fine to fine droplets)
2.25	79	46	
3.75	128	75	
8	253	157	

Ground applications result in less spray drift than aerial applications in general. For the most sensitive species, cucumber, applications at 8 lb ae/A result in buffer distances of 253 ft for ground application and over 1,000 ft for aerial application. Applications at rates of 3.75 lb ae/A result in much lower buffer distances (128 ft for ground application and 466 ft for aerial application).

Aquatic Risks

To assess potential risk to aquatic organisms, the EPA reviewed both registrant-submitted studies and open literature studies. The EPA also assessed risk from exposure to technical grade glyphosate and for formulated glyphosate, including formulations containing polyoxyethylene tallow amine (POEA). While POEA is not used in glyphosate formulations labeled for aquatic use sites, terrestrial formulations may still contain POEA and may contribute to exposure via runoff. Risk from runoff and spray drift were assessed. Exposure from both terrestrial and aquatic applications were considered.

Data on the degradate aminomethylphosphonic acid (AMPA) were available for fish and aquatic invertebrates and were reviewed as part of the aquatic assessment. Based on existing data,

AMPA appears to be less acutely toxic to aquatic organisms than the parent glyphosate and the existing aquatic assessment is considered protective for exposure to AMPA.

Fish, Aquatic Invertebrates, and Aquatic-Phase Amphibians

Risks to fish, aquatic invertebrates, and aquatic-phase amphibians did not exceed the LOC for exposure to glyphosate alone (acute RQs < 0.01, where the acute LOC = 0.5; chronic RQs ≤ 0.12, where the chronic LOC = 1). Risks are also likely to be low for exposure to formulations containing POEA (acute RQs ≤ 0.07). Formulations that do not contain POEA similarly did not show risks of concern (acute RQs < 0.01).

Aquatic Vascular and Non-Vascular Plants

Risks to aquatic plants did not exceed the level of concern for exposure to glyphosate alone (acute RQs ≤ 0.17, where the LOC=1). Risks are likely to be low for exposure to formulations containing POEA via terrestrial applications (acute RQs ≤ 0.68). Risks exceed the level of concern for exposure to formulations without POEA for applications to aquatic environments (acute RQs ≤ 2.6). This is not surprising, given that some glyphosate formulations are tailored to treat aquatic weeds.

Evaluation of risk to terrestrial plants from exposure to spray drift via glyphosate formulations is described in the terrestrial plant section, and the calculated distances off-field to be below toxicity threshold would apply to emergent aquatic vegetation as well as terrestrial plants. For emergent aquatic vascular plants, there is potential for risk from exposure to spray drift from terrestrial uses (distance from the edge of the field to below toxicity threshold is over 1,000 ft, for application rates at 8 lb ae/A, see table 2).

2. Ecological Incidents

A review of the Ecological Incident Information System (EIIS) and the Avian Monitoring Information System (AIMS) was conducted on February 21, 2014. A search of the Office of Pesticide Incident Data system (IDS) for aggregated incidents (i.e., registrant-reported incidents) was conducted on February 27, 2014. Incidents in EIIS are classified as “possible,” “probable,” and “highly probable.” Incidents in AIMS are classified as “possible,” “probable,” “likely,” “highly likely,” and “certain.” The majority of the glyphosate incidents are for terrestrial plants, fewer incidents were reported for terrestrial and aquatic wildlife.

Terrestrial plant incidents

Plant incidents for glyphosate and its various salt forms involved either direct treatment or spray drift and resulted in either plant damage or mortality. Approximately 602 individual plant incidents were reported, and 724 aggregate incidents were reported. Reports were classified from “possible” to “highly probable.” Most plant incidents involved spray drift onto adjacent agricultural crops and grass. There were a few incidents of trees being damaged or killed. There was one incident which involved use on a right-of-way that was classified as highly probable.

Terrestrial wildlife incidents

Five wildlife incidents were reported for glyphosate for uses on rangeland/pasture, home/lawn, and a tree farm. One consisted of accidental misuse on corn where an unknown bird was reported as dead. Two incidents classified as “possible” involved mortality to three birds from drift and mortality to several dogs from runoff. No additional details were provided for the dog mortalities. For the bird mortalities, other chemicals were applied at the same time, including atrazine, s-metolachlor, and permethrin. One incident involved honeybees and was classified as “possible” where it was reported that an herbicide containing sulfometuron methyl and glyphosate was applied near flowering areas and twitching or dead bees were observed near three hives. One “probable” incident reported incapacitation of two iguanas following ingestion of dandelions sprayed with glyphosate. In the IDS aggregate database, there were 38 reports of wildlife incidents, but additional details were not available.

Aquatic incidents

One “possible” 2003 incident involved 10 dead goldfish, 2 incapacitated fish, and other fish observed “gasping” at the water surface; investigators reported it was not possible to determine a reason for the fish kill due to lack of water measurements. Eleven fish incidents were reported from 1990 to 2003 with classifications ranging from “possible” to “highly probable.” One “highly probable” incident involved misuse where thousands of shad were killed. Four other incidents of misuse were also reported. Two fish kill incidents were reported where glyphosate was applied directly to the fish pond, in both cases investigations indicated that elevated ammonia and reduced dissolved oxygen may have been reason for the fish kill. One incident involved glyphosate being applied to the perimeter of a pond and fish kills were reported 2 months later; the report indicated that overstocking and improper dissolved oxygen may have killed the fish. In one incident, glyphosate was applied to 80 acres next to a fish pond, when it rained the next day, 700 fish were found dead, but no other details were provided.

Incident update

As of 2017, all ecological incidents are migrated and combined into IDS. An updated search for new ecological incidents since 2014 was conducted in IDS on November 26, 2018. There were 24 reported incidents of on-site crop damage from application of glyphosate in combination with other pesticides. Twelve incidents were on treated corn and were classified as “possible” to “probable”; the adverse effects observed in corn included crop injury, discoloration, or death. There were 12 incidents of crop damage on soybean, incident classifications ranged from “possible” to “probable” and adverse effects observed were browning/death or discoloration/bleaching.

There were 5 reported incidents of off-target spray drift damage. One “probable” incident in 2014 involved drift onto a nearby vineyard from a non-crop area application nearby and resulted in the withering and yellowing of grape leaves. Another “possible” incident in 2014 involved dead or dying bees on a sidewalk from application of glyphosate and pendimethalin in the area; no further details were provided. A “possible” incident in 2015 involved drift from a glyphosate ditch area application which resulted in death in 7 bee hives nearby a week later; the beekeeper reported loss of over 100,000 bees. Another “probable” incident in 2015 involved drift from a

field corn application which resulted in phytotoxicity in a garden nearby. A “possible” incident in 2017 involved drift damage to 20 acres of roses and 22 thousand potted roses; multiple herbicide applications were reported nearby by multiple growers.

3. Ecological and Environmental Fate Data Needs

The ecological effects data required as part of the glyphosate registration review DCI were received and found to be adequate for risk assessment. As noted in Table 1, pollinator data may still be needed. The agency will issue a DCI for pollinator data as part of a separate action if it determines that additional pollinator data are necessary to help make a final registration review decision for glyphosate.

C. Risk Characterization

Birds and Mammals

Potential risks were identified for mammals and birds feeding on foliar dietary items treated with glyphosate. There were marginal risk exceedances for applications at the maximum single aerial application rate of 1.55 lb ae/A, the maximum single ground application rate of 3.75 lb ae/A, application to sugarcane, and applications to tree crops, forests, pastures, and non-crop areas at 8 lb ae/A. Risks from these scenarios are likely limited to the treated field and areas near the treated field. Risk to mammals and birds were primarily for application as spot treatment. Spot treatments are limited to residential areas and limited to small areas, so risks from this use are likely spatially limited. In addition, the risk assessment assumes that birds and mammals will consume food items treated with glyphosate as 100% of their diet, this is unlikely to occur from spot treatment application.

According to USDA, use on non-food tree crops, forestry, pastures, and non-crop areas are also geographically limited.¹⁰ The high application rate of 8 lb ae/A intended for these uses are for small spot treatments in highly concentrated and localized areas for management of invasive weeds and for conservation purposes on non-agricultural lands. The application methods used for these sites are unlikely to drive drift, as application is usually by small mechanically-pressurized or handheld equipment. Exposure to birds and mammals under such conditions are likely to be localized and minimal.

Non-food tree crop applications are intended for private forestry management. According to USDA, glyphosate is applied in this setting as part of a tank mix for weed resistance management, and the rate used is no more than 4.5 or 5 lbs ae/A. Application for forestry management is usually made by helicopter equipped with drift control technologies, including micro-foil boom and raindrop nozzles which allow for precise applications. Glyphosate is also applied to conifer and hybrid cottonwood establishments in the Pacific Northwest, and recommended use rates for site preparation range from 1.5 to 3 lb ae/A.

¹⁰ See USDA's comments on the glyphosate ecological risk assessment in the glyphosate registration review docket at: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-1618>

Glyphosate use in pastures is for renovation and habitat restoration efforts. According to USDA, glyphosate is applied at 2.25 lb ae/A for forage renovation (to convert common bermudagrass to hybrid bermudagrass) with 2 consecutive fall applications. In natural areas or utility rights of way, glyphosate rates may reach 4 lb ae/A. Application above 4 lb ae/A is usually applied by handgun for spot treatment of invasive weeds, such as cogon grass, and are not likely to drive risk concerns.

Since these uses are very localized and application to these use sites are either with lower application rates than assessed or done with application equipment that is unlikely to contribute to spray drift, risk to mammals and birds from these uses is expected to be lower than estimated.

Terrestrial and Aquatic Plants

Consistent with its mode of action as an herbicide, risk to non-target terrestrial and aquatic plants were primarily from spray drift and the resulting buffer distances were heavily dependent on the application rate used (Table 2). The maximum labeled single application rate for ground application to agricultural row crops is 3.75 lb ae/A; at this rate, the distance from the edge of the field to get below toxicity threshold is 128 ft. The maximum labeled single application rate for aerial application to agricultural row crops is 1.55 lb ae/A; at this rate, the distance from the edge of the field to get below toxicity threshold is 190 ft.

The EPA recently completed an updated analysis of glyphosate usage (see the *Glyphosate: Response to Comments, Usage, and Benefits* document), and data from 2012 to 2016 indicate that for many crops, the average single application rates used by growers are even lower than the application rates assessed by the EPA for ground and aerial row crop applications. Average single application rates used by growers vary from crop to crop but range from 0.67 lb ae/A for canola to 1.84 lb ae/A for table grapes. The majority of glyphosate is applied to corn (approximately 94.9 million lb ae applied annually) and soybean (approximately 113.9 million lb ae applied annually). The average single application rate used for corn is 0.95 lb ae/A and the average single application rate used for soybean is 0.97 lb ae/A. If average application rates are close to typical grower practices, spray drift risk to non-target terrestrial and aquatic plants from row crop applications is expected to be lower than estimated.

For detailed crop by crop usage and rate information, see the *Glyphosate: Response to Comments, Usage, and Benefits* document in the glyphosate docket at www.regulations.gov.

Aquatic Uses

USDA submitted additional information on aquatic applications of glyphosate (2018). Application of glyphosate in aquatic use sites at rates of 8 lb ae/A are for perennial grass control (ex., the invasive torpedograss in Florida). Application at the 8 lb ae/A rate occurs only once per site per year, and aerial applications in such instances are atypical. Perennial grasses like *Arundo* (giant reed) and *Phragmites* (common reed) can be controlled with lower rates and with one application per year. Programs to control giant salvinia (an invasive aquatic fern) in Louisiana involve multiple applications of glyphosate at 1-2 lb ae/A, up to the yearly maximum of 8 lb ae/A. As such, risk to non-target organisms from application to aquatic use sites would be geographically limited.

To view the information submitted from USDA on the non-agricultural uses described previously, please visit the glyphosate public docket at www.regulations.gov (EPA-HQ-OPP-2009-0361-1618).

D. Benefits Assessment

Glyphosate is the most commonly used agricultural herbicide in the United States, in terms of area treated. It is a broad-spectrum herbicide that controls broadleaf, sedge, and grass weeds with minimal residual toxicity to crops or non-target vegetation. Glyphosate is a unique herbicide as it is the only herbicide classified as a Group 9 herbicide by the Weed Science Society of America (WSSA). Glyphosate is a relatively inexpensive herbicide to apply in agricultural situations, with the cost of applications to most crops ranging \$1 to \$13 per acre.

Glyphosate is registered for use in agriculture, including horticulture, viticulture, and silviculture, as well as non-agricultural sites including commercial, industrial, and residential areas. Current glyphosate-resistant field crops include soybean, corn, cotton, canola, alfalfa, and sugar beet. Many of these crops, such as corn, cotton, soybean, and sugar beet, have exceptionally high percentages of their acreage treated with glyphosate (approximately 90 percent of acres treated in each crop). Genetically-engineered (transgenic) glyphosate-resistant (GR) varieties of these crops can be sprayed over-the-top with minimal or no crop phytotoxicity, and glyphosate may also be used as a pre-plant burndown in many of these crops. On average, 84 percent of glyphosate applied in agricultural settings, in terms of pounds, is applied to soybeans, corn, or cotton per year.

Glyphosate is also beneficial as part of weed control programs in orchards and specialty crops. Glyphosate use is prevalent in orchard and vineyards floor management and most acres of crops such as tree nuts, citrus, and grapes are treated with glyphosate. Glyphosate is the most diverse herbicide in orchard floor management because it may be used for under tree weed control, chemical wiping, chemical mowing, and spot treatment. Since glyphosate controls a broad spectrum of weeds and does not have residual soil activity, it can be used to control emerged weeds prior to planting high value crops such as fruits and vegetables, where growers sometimes have limited weed control options.

Glyphosate is also important for noxious and invasive weed control in aquatic systems, pastures/rangelands, public lands, forestry, and rights-of-ways. Invasive weeds controlled by glyphosate include cattails and water hyacinth, which can impede water flow and impede irrigation. Improper weed management can cause water to stagnate, which provides a breeding habitat for mosquitos, therefore effective weed control is important for controlling mosquito-borne diseases. Glyphosate is also important for habitat restoration efforts. It is used to control invasive annual, perennial, and woody plants in riparian habitats and rangeland. Glyphosate use in rights of ways helps keep roadways and railroad tracks safe by protecting the stability of the surface, maintaining visibility for operators, and allowing for the distribution of goods, services, and utilities (gas and electric). Glyphosate is the top active ingredient used to control invasive species in the United States.

Glyphosate is a versatile active ingredient and can be applied with many different types of application equipment depending on the needs of the user. In addition to the broadcast spray applications, it can be applied via application methods such as cut stump treatment, stem/tree injection, wick applications, spot treatment, under hooded sprayers, and as a directed spray.

For more information on the benefits of glyphosate, see the *Glyphosate: Response to Comments, Usage, and Benefits* and the 2018 comment from USDA in the glyphosate public docket (EPA-HQ-OPP-2009-0361-1618).

IV. PROPOSED INTERIM REGISTRATION REVIEW DECISION

A. Proposed Risk Mitigation and Regulatory Rationale

The EPA did not identify any human health risks from exposure to any use of glyphosate. The agency identified potential risk to mammals and birds, however these risks are expected to be limited to the application area or areas near the application area. The EPA identified potential risk to terrestrial and aquatic plants from off-site spray drift, consistent with glyphosate's use as a herbicide.

Glyphosate is a versatile herbicide that provides a broad spectrum of weed control across numerous agricultural and non-agricultural sites. Glyphosate is generally inexpensive in agricultural settings. Glyphosate is important in the management of invasive/noxious weeds and is essential in habitat restoration efforts for rangeland and pastures. It is used for weed management for rights-of-ways, forestry, industrial settings, residential areas, and aquatic environments.

The EPA concludes that the benefits outweigh the potential ecological risks when glyphosate is used according to label directions. To reduce off-site spray drift to non-target organisms, the EPA is proposing certain spray drift management measures. To preserve glyphosate as a viable tool for growers and combat weed resistance, the EPA is also proposing that herbicide resistance management language be added to all glyphosate labels. The EPA is also proposing certain labeling clean-up/consistency efforts to bring all glyphosate labels up to modern standards. The EPA has discussed these measures with the Joint Glyphosate Task Force, a registrant consortium, which does not oppose the proposed risk mitigation outlined herein.

1. Spray Drift Management

The agency is proposing label changes to reduce off-target spray drift and establish a baseline level of protection against spray drift that is consistent across all glyphosate products. Reducing spray drift will reduce the extent of environmental exposure and risk to non-target plants and animals. Although the agency is not making a complete endangered species finding at this time, these label changes are expected to reduce the extent of exposure and may reduce risk to listed species whose range and/or critical habitat co-occur with the use of glyphosate.

The agency is proposing the following spray drift mitigation language to be included on all glyphosate product labels for products applied by liquid spray application. The proposed spray drift language is intended to be mandatory, enforceable statements and supersede any existing language already on product labels (either advisory or mandatory) covering the same topics. The agency is providing recommendations which allow glyphosate registrants to standardize all advisory language on glyphosate product labels. Registrants must ensure that any existing advisory language left on labels does not contradict or modify the new mandatory spray drift statements proposed in this PID, once effective.

- Applicators must not spray during temperature inversions.
- For aerial applications, do not apply when wind speeds exceed 15 mph at the application site. If the wind speed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor blade diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.
- For aerial applications, the release height must be no higher than 10 feet from the top of the crop canopy or ground, unless a greater application height is required for pilot safety.
- For ground boom applications, apply with the release height no more than 4 feet above the ground or crop canopy.
- For ground and aerial applications, select nozzle and pressure that deliver “fine” or coarser droplets as indicated in nozzle manufacturers’ catalogues and in accordance with American Society of Agricultural & Biological Engineers Standard 572.1 (ASABE S572.1).

The Agency’s goal is to manage off-target spray drift from applications of glyphosate while continuing to preserve glyphosate’s utility for growers and allow growers continued flexibility when making applications. The agency assessed the potential impact on growers of the proposed spray drift management restrictions and has determined that these measures are not expected to substantially reduce the benefit of glyphosate to users. Prohibiting glyphosate applications during temperature inversions may impact the usability of glyphosate products by reducing the amount of time users have to apply glyphosate, but growers can switch to other products if they encounter temperature inversions.

The EPA considered the impact of requiring “fine” or coarser droplets (*i.e.*, requiring growers to deliver droplets no smaller than “fine”) on glyphosate labels and has determined that such a requirement is not likely to affect the efficacy of glyphosate when used alone since it is systemic. Glyphosate is a compound that is frequently tank mixed with other herbicides. Because the proposed language provides flexibility with droplet size for tank mixed partners, the EPA does not expect there would be concerns for tank mixing with other herbicides. However, since glyphosate can be applied as a burndown treatment, insecticides may be included in the tank mix. Insecticides are generally considered to provide better efficacy with smaller droplets. The EPA is uncertain if requiring “fine” or coarser droplets will impact the efficacy of insecticides tank mixed with glyphosate because some insecticides could be more effective at droplet sizes smaller than “fine” (such as “very fine” or “extremely fine”). If reduced efficacy occurred, the agency would expect growers to respond by increasing the application rates (if allowed by the label), increasing the number of applications, increasing the application rates of tank mix partners, making additional applications, or switching to a different active ingredient.

In addition to including the spray drift restrictions on glyphosate labels, all references to volumetric mean diameter (VMD) information for spray droplets are proposed to be removed from all glyphosate labels where such information currently appears. The proposed new language above, which cites ASABE S572.1, eliminates the need for VMD information. The agency is also proposing the addition of a non-target organism advisory statement. The protection of pollinating organisms is a priority for the agency. It is possible that pollinators and other non-target organisms may be indirectly impacted from effects on forage and habitat. It is the agency's goal to reduce spray drift whenever possible and to educate growers on the potential for indirect effects on the forage and habitat of pollinators and other non-target organisms. Therefore, the EPA is proposing non-target organism advisory language to be placed on glyphosate labels to address this potential concern.

2. Herbicide Resistance Management

On August 24, 2017, the EPA finalized a Pesticide Registration Notice (PRN) on herbicide resistance management.¹¹ Consistent with the Notice, the EPA is proposing the implementation of herbicide resistance measures for existing chemicals during registration review, and for new chemicals and new uses at the time of registration. In registration review, herbicide resistance elements will be included in every herbicide PID.

The development and spread of herbicide resistant weeds in agriculture is a widespread problem that has the potential to fundamentally change production practices in U.S. agriculture. While herbicide resistant weeds have been known since the 1950s, the number of species and their geographical extent, has been increasing rapidly. Currently there are over 250 weed species worldwide with confirmed herbicide resistance. In the United States, there are over 155 weed species with confirmed resistance to one or more herbicides.

Management of herbicide resistant weeds, both in mitigating established herbicide resistant weeds and in slowing or preventing the development of new herbicide resistant weeds, is a complex problem without a simple solution. Coordinated efforts of growers, agricultural extension, academic researcher, scientific societies, pesticide registrants, and state and federal agencies are required to address this problem.

The EPA is requiring measures for the pesticide registrants to provide growers and users with detailed information and recommendations to slow the development and spread of herbicide resistant weeds. This is part of a more holistic, proactive approach recommended by crop consultants, commodity organizations, professional/scientific societies, researchers, and the registrants themselves.

3. Non-target Organism Advisory Statement

The protection of pollinators and other non-target organisms is a priority for the agency. While the agency did not identify risks to individual bees from glyphosate applications at rates below 5.7 lb ae/A, risks to terrestrial invertebrates at higher application rates are uncertain. In addition,

¹¹ PRN 2017-2, "Guidance for Herbicide Resistance Management Labeling, Education, Training, and Stewardship"

glyphosate may impact non-target plants via spray drift and impact nectar sources and habitat for pollinators and other non-target organisms. EPA is proposing a non-target organism advisory statement to alert users of potential impact to non-target organisms: "This product is toxic to plants and may adversely impact the forage and habitat of non-target organisms, including pollinators, in areas adjacent to the treated site. Protect the forage and habitat of non-target organisms by following label directions intended to minimize spray drift."

4. Label Consistency Measures

There are currently 555 Section 3 registrations and 37 Section 24(c) registrations for glyphosate. Labels directions for glyphosate vary significantly from label to label, and newer stamped labels in general have better instructions than older labels. The EPA is proposing to update all glyphosate labels to modern standards. The components of the label the agency proposes to update are as follows: the maximum application parameters, the environmental hazards statement for aquatic use, and clarification on rotational crop timing. In addition, the agency is providing guidance to glyphosate registrants on acceptable marketing statements.

Maximum Application Parameters

In 2013, at the agency's request and in preparation for risk assessment, the Joint Glyphosate Task Force, a consortium of glyphosate registrants, created a *Use Summary Matrix*, which was intended to summarize all use sites being supported as part of registration review and outline important application parameters such as maximum single and yearly application rates. EPA's risk assessments for glyphosate were based on maximum application parameters as described in the *Use Summary Matrix*. EPA is proposing that maximum labeled rates on current labels be consistent with the maximum application rates that were assessed by the agency and supported by the Joint Glyphosate Task Force. These maximum application parameters are described in Appendix C of this document.

Many older glyphosate labels do not define any maximum application parameters. EPA proposes that maximum application parameters be clearly defined and must not exceed the maximum application parameters as described in Appendix C. It is not EPA's intention to change the current application rates on glyphosate labels, but the agency is proposing to define the rate limits in order to establish better consistency and clarity on labels. Appendix C lists the maximum application parameters by use site for both aerial and ground application.

Statements for Aquatic Uses

The EPA is proposing to update the environmental hazards statements for aquatic use products to be consistent with modern standards and to be in line with newer pesticide labels. The glyphosate Reregistration Eligibility Decision (RED) issued in 1993 specified that glyphosate labels formulated for aquatic use have language intended to warn users of potential fish suffocation for aquatic applications. The EPA is proposing to update the existing language to be consistent with current labeling guidelines (see the EPA's Label Review Manual). Proposed environmental hazards statements are listed in table 4.

In addition, the agency is proposing an additional statement under “directions for use” for aquatic use labels to instruct users to apply in strips to help avoid oxygen depletion when emerged weed infestations cover the total surface area of an impounded water body; the proposed statement also appears in table 4. These statements already appear on some newer labels and the agency is proposing to apply these statements to all labels.

Table 4. Proposed Statements for Glyphosate for Aquatic Use

Product Type	Proposed Statement
Environmental hazards: for labels with terrestrial uses only	“Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Environmental hazards: for labels with aquatic uses only	“Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Environmental hazards: for labels with both aquatic and terrestrial uses	“Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. For terrestrial uses, do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark [Optional text, if applicable: except when applying this product by air over the forest canopy]. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Directions for use for aquatic uses	“When emerged weed infestations cover the total surface area of an impounded waterbody, apply this product to the emerged vegetation in strips to help avoid oxygen depletion in the water due to decaying vegetation. Oxygen depletion in the water can result in increased fish mortality.”

Clarification on Rotational Crop Timing

Many glyphosate labels lack instructions for crop rotation. The EPA is proposing to clarify that treated fields may be rotated to a labeled crop at any time. For fields being rotated to a non-labeled crop, any glyphosate application must be made a minimum of 30 days prior to planting.

Label Claims

During meetings with the agency in 2018, the Joint Glyphosate Task Force proposed to clarify on existing labels a statement about how glyphosate works. The following statement is proposed: “Glyphosate works by targeting an enzyme that is essential for plant growth.” The proposed revision is consistent with the requirements of 40 CFR § 156.10(a)(5). Registrants may use alternate claims, as long as alternate claims meet labeling requirements. Registrants can refer to 40 CFR § 156.10(a)(5) for requirements regarding label claims prior to submitting updated labels for registration review.

B. Tolerance Actions

The EPA is proposing that the number of significant figures be modified for several tolerances, and that new tolerances be established for various vegetable and fruit groups and subgroups. The new tolerance groupings remove the need for certain older tolerances, which are proposed to be deleted. The Agency will issue a Federal Register notice announcing these proposed tolerance changes under FFDCA following issuance of an Interim Decision for glyphosate. Refer to section III.A.3 of this document for the proposed tolerance changes.

C. Proposed Interim Registration Review Decision

In accordance with 40 CFR § 155.56 and 155.58, the agency is issuing this Proposed Interim Registration Review Decision. Except for the EDSP, ESA and pollinator components of this case, the agency has made the following Proposed Interim Registration Review Decision: (1) no additional data are required at this time; and (2) changes to the affected registrations and their labeling are needed at this time, as described in Section IV. A. and Appendices B and C.

In this proposed interim registration review decision, the EPA is making no human health or environmental safety findings associated with the EDSP screening of glyphosate, nor is it making a complete endangered species finding or a complete assessment of effects to pollinators. Although the agency is not making a complete endangered species finding at this time, the proposed mitigation described in this document is expected to reduce the extent of environmental exposure and may reduce risk to listed species whose range and/or critical habitat co-occur with the use of glyphosate. The agency's final registration review decision for glyphosate will be dependent upon the result of the agency's ESA assessment and any needed Section 7 consultation with the Services, an EDSP FFDCA section 408(p) determination, and an assessment of non-target exposure to pollinators (bees).

D. Data Requirements

No additional data are required as part of this proposed interim registration review decision. The EPA will consider requesting the glyphosate registrants to submit pollinator data as a separate action.

V. NEXT STEPS AND TIMELINE

A. Proposed Interim Registration Review Decision

A Federal Register Notice will announce the availability of this proposed interim registration review decision for glyphosate and will allow a 60-day comment period on the proposed interim decision. If there are no significant comments or additional information submitted to the docket during the comment period that leads the agency to change its proposed interim decision, the EPA may issue an interim registration review decision for glyphosate. However, a final decision for glyphosate may be issued without the agency having previously issued an interim decision. A

final decision on the glyphosate registration review case will occur after: 1) an EDSP FFDCA section 408(p) determination, 2) an endangered species determination under the ESA and any needed Section 7 consultation with the Services, and 3) a more in-depth assessment of non-target exposure to pollinators, if determined to be necessary.

B. Implementation of Mitigation Measures

Once the Interim Registration Review Decision is issued the glyphosate registrants must submit amended labels that include the label changes described in Appendices A, B, and C. The revised labels must be submitted to the agency for review within 60 days following issuance of the Interim Registration Review Decision.

Appendix A: Summary of Proposed Actions for Glyphosate

Registration Review Case#: 0178

PC Codes: 103601, 103604, 103605, 103607, 103608, 103613, 417300

Chemical Type: herbicide

Chemical Family: glycine derivative

Mode of Action: targets the 5-enolpyruvyl-3-shikimate phosphate synthase enzyme

Affected Population(s)	Source of Exposure	Route of Exposure	Duration of Exposure	Potential Risk(s) of Concern	Proposed Actions	Comment (used to briefly clarify or elaborate on risk or mitigation)
Terrestrial and aquatic plants	Spray drift	Foliar absorption	Acute Chronic	Survival, biomass	Require enforceable spray drift management language; updated environmental hazards language	
Birds	Residues on food items (via deposition or spray drift)	Dietary	Acute Chronic	Growth	Require enforceable spray drift management language	Risks are likely limited to the field and areas near the application field.
Mammals	Residues on food items (via deposition or spray drift)	Dietary	Acute Chronic	Growth and reproduction	Require enforceable spray drift management language	Risks to are likely limited to the field and areas near the application field.
Terrestrial invertebrates	Residues on nectar sources (via deposition or spray drift)	Dietary	Acute Chronic	Effects on nectar sources of terrestrial invertebrates	Non-target organism environmental hazards language	Risks to bees are uncertain at application rates higher than 5.7 lb ae/A. The agency may require additional pollinator data to fully assess risk to terrestrial invertebrates.

Appendix B: Proposed Labeling Changes for Glyphosate Products

Description	Proposed Label Language for Glyphosate Products				Placement on Label
	End Use Products				
Mode/Mechanism of Action Group Number					Front Panel, upper right quadrant. All text should be black, bold face and all caps on a white background, except the mode of action code, which should be white, bold face and all caps on a black background; all text and columns should be surrounded by a black rectangle.
	Glyphosate	GROUP	9	HERBICIDE	
Non-target Organism Advisory Statement	“NON-TARGET ORGANISM ADVISORY STATEMENT: This product is toxic to plants and may adversely impact the forage and habitat of non-target organisms, including pollinators, in areas adjacent to the treated site. Protect the forage and habitat of non-target organisms by following label directions intended to minimize spray drift.”				Environmental Hazards
Environmental Hazards Statement for Aquatic Use	<i>For labels without aquatic uses:</i> “Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.” <i>For labels with aquatic uses only:</i> “Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.” <i>For labels with both aquatic and terrestrial uses:</i> “Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. For terrestrial uses, do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark [Optional text, if applicable: except when applying this product by air				Environmental Hazards

Description	Proposed Label Language for Glyphosate Products	Placement on Label
	over the forest canopy]. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”	
Aquatic Use Statement	“When emerged weed infestations cover the total surface area of an impounded waterbody, apply this product to the emerged vegetation in strips to help avoid oxygen depletion in the water due to decaying vegetation. Oxygen depletion in the water can result in increased fish mortality.”	Directions for Use
HERBICIDE RESISTANCE MANAGEMENT: Weed Resistance Management	Include resistance management label language for herbicides from PRN 2017-1 and PRN 2017-2 (https://www.epa.gov/pesticide-registration/pesticide-registration-notice-year)	Directions for Use, prior to directions for specific crops under the heading “WEED RESISTANCE-MANAGEMENT”
Additional Required Labelling Action (Applies to all products delivered via liquid spray applications)	Remove information about volumetric mean diameter from all labels where such information currently appears.	Directions for Use
Rotational crop information	“Treated fields may be rotated to a labeled crop at any time. For treated fields being rotated to a non-labeled crop, application must be made a minimum of 30 days prior to planting.”	Directions for Use
Label claims	“Glyphosate works by targeting an enzyme that is essential for plant growth.” [Alternate claims, if used, must meet labeling requirements. Refer to 40 CFR § 156.10(a)(5) for requirements regarding label claims.]	Product Information

Description	Proposed Label Language for Glyphosate Products	Placement on Label
Clarification of application rates	Ground and aerial applications rates on the labels must not exceed the maximum application parameters as noted in Appendix C of this document, which were maximum application parameters assessed by the EPA. Application rates may only be clarified for uses that are currently approved on labels.	Directions for Use
Mandatory Spray Drift Management Language for all products delivered via liquid spray application and allow aerial application	“SPRAY DRIFT <u>Aerial Applications:</u> • Do not release spray at a height greater than 10 ft above the ground or vegetative canopy, unless a greater application height is necessary for pilot safety. • Applicators are required to use a fine or coarser droplet size (ASABE S572.1). • Applicators must use ½ swath displacement upwind at the downwind edge of the field. • Do not apply when wind speeds exceed 15 mph at the application site. If the windspeed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters. • Do not apply during temperature inversions.”	Directions for Use, in a box titled “Spray Drift” under the heading “Aerial Applications,” and before use rates and or application instructions
Enforceable Spray Drift Management Language for products that allow airblast applications	“SPRAY DRIFT <u>Airblast Applications:</u> • Sprays must be directed into the canopy. • Do not apply when wind speeds exceed 15 miles per hour at the application site. • User must turn off outward pointing nozzles at row ends and when spraying outer rows. • Do not apply during temperature inversions.”	Directions for Use, in a box titled “Spray Drift” under the heading “Airblast Applications”
Enforceable Spray Drift Management Language for products that are applied as liquids and allow ground boom applications	“SPRAY DRIFT <u>Ground Boom Applications:</u> • User must only apply with the release height recommended by the manufacturer, but no more than 4 feet above the ground or crop canopy. • Applicators are required to use a fine or coarser droplet size (ASABE S572.1). • Do not apply when wind speeds exceed 15 miles per hour at the application site. • Do not apply during temperature inversions.”	Directions for Use, in a box titled “Spray Drift” under the heading “Ground Boom Applications”

Enforceable Spray Drift Management Language for products that are applied as liquids and allow boom-less ground sprayer applications	“SPRAY DRIFT Boom-less Ground Applications: • Applicators are required to use a fine or coarser droplet size (ASABE S572.1) for all applications. • Do not apply when wind speeds exceed 15 miles per hour at the application site. • Do not apply during temperature inversions.”	Directions for Use, in a box titled “Spray Drift” under the heading “Boom-less Applications”
Advisory Spray Drift Management Language for all products delivered via liquid spray application	“SPRAY DRIFT ADVISORIES THE APPLICATOR IS RESPONSIBLE FOR AVOIDING OFF-SITE SPRAY DRIFT. BE AWARE OF NEARBY NON-TARGET SITES AND ENVIRONMENTAL CONDITIONS. IMPORTANCE OF DROPLET SIZE An effective way to reduce spray drift is to apply large droplets. Use the largest droplets that provide target pest control. While applying larger droplets will reduce spray drift, the potential for drift will be greater if applications are made improperly or under unfavorable environmental conditions. Controlling Droplet Size – Ground Boom <i>(note to registrants: remove if ground boom is prohibited on product labels)</i> • Volume - Increasing the spray volume so that larger droplets are produced will reduce spray drift. Use the highest practical spray volume for the application. If a greater spray volume is needed, consider using a nozzle with a higher flow rate. • Pressure - Use the lowest spray pressure recommended for the nozzle to produce the target spray volume and droplet size. • Spray Nozzle - Use a spray nozzle that is designed for the intended application. Consider using nozzles designed to reduce drift. Controlling Droplet Size – Aircraft <i>(note to registrants: remove if aerial application is prohibited on product labels)</i> • Adjust Nozzles - Follow nozzle manufacturers’ recommendations for setting up nozzles. Generally, to reduce fine droplets, nozzles should be oriented parallel with the airflow in flight. BOOM HEIGHT – Ground Boom <i>(note to registrants: remove if ground boom is prohibited on product labels,</i> For ground equipment, the boom should remain level with the crop and have minimal bounce. RELEASE HEIGHT - Aircraft <i>(note to registrants: remove if aerial application is prohibited on product labels)</i> Higher release heights increase the potential for spray drift. SHIELDED SPRAYERS	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”

	Shielding the boom or individual nozzles can reduce spray drift. Consider using shielded sprayers. Verify that the shields are not interfering with the uniform deposition of the spray on the target area. TEMPERATURE AND HUMIDITY When making applications in hot and dry conditions, use larger droplets to reduce effects of evaporation. TEMPERATURE INVERSIONS Drift potential is high during a temperature inversion. Temperature inversions restrict vertical air mixing, which can cause small droplets to remain suspended in a concentrated cloud. This cloud can move in unpredictable directions due to the light variable winds common during inversions. Temperature inversions are characterized by increasing temperatures with altitude and are common on nights with limited cloud cover and light to no wind. They can begin to form in late afternoon/early evening and often continue into the morning. Their presence can be indicated by ground fog. If fog is not present, inversions can also be identified by the movement of smoke from a ground source or an aircraft smoke generator. Smoke that layers and moves laterally in a concentrated cloud (under low wind conditions) indicates an inversion, while smoke that moves upward and rapidly dissipates indicates good vertical air mixing. WIND Drift potential generally increases with wind speed. AVOID APPLICATIONS DURING GUSTY WIND CONDITIONS. Applicators need to be familiar with local wind patterns and terrain that could affect spray drift.”	
Advisory Spray Drift Management Language for products that are applied as liquids and allow boom-less ground sprayer applications	“SPRAY DRIFT <u>Boom-less Ground Applications:</u> • Setting nozzles at the lowest effective height will help to reduce the potential for spray drift.”	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”
Advisory Spray Drift Management Language for all products that allow liquid applications with handheld technologies	“SPRAY DRIFT <u>Handheld Technology Applications:</u> • Take precautions to minimize spray drift.”	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”

Appendix C. Proposed Maximum Application Rates for Glyphosate Ground and Aerial Application

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Round-up Ready 2 Yield Soybeans	3.75	1.55	6
Root Tuber Vegetables: arracacha, arrowroot, carrot, chinese artichoke, Jerusalem artichoke, beet (garden), burdock, canna, cassava (bitter and sweet), celeriac, chayote (root), chervil (turnip-rooted), chicory, chufa, dasheen (taro), galangal, ginger, ginseng, horseradish, leren, kava (turn-rooted), parsley (turnip-rooted), parsnip, potato, radish, rutabaga, oriental radish, salsify, skirret, sweet potato, tanier, turmeric, turnip, wasabi, yacon, yam bean, true yam	3.75	1.55	6
Rangelands	0.38	0.38	2.25
Pome Fruits: including apple, crabapple, loquat, mayhaw, pear, oriental pear, quince	3.75	1.55	8
Pastures	8	8	8
Oilseed Crops: borage, buffalo gourd, calendula, canola, castor oil plant, chinese tallow tree, crambe, cuphea, echium, euphorbia, evening primrose, flax (seed), gold of pleasure, hare's ear mustard, jojoba, lesquerella, meadow foam, milkweed, mustard (seed), niger (seed), oil radish, poppy seed, rapeseed, rose hip, safflower, sesame, stokes aster, sunflower, sweet rocket, tallow wood, tea oil plant, veronia.	3.75	1.55	6
Non-Food Tree Crops: pine, poplar, eucalyptus, christmas trees, other non-food tree crops	8	8	8
Miscellaneous Tree Food Crops: cactus (fruit and pads), palm (heart, leaves, oil)	3.75	1.55	8
Miscellaneous Crops: aloe vera, bamboo shoots, globe artichoke, okra, peanut (ground nut), strawberry, sugar beet, asparagus, pineapple	3.75	1.55	6
Legume Vegetables: Succulent varieties of Bean (Lupinus: includes grain lupin, sweet lupin, white lupin, white sweet lupin); Bean (Phaseolus: includes field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean, wax bean); Bean (Vigna: includes adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, yardlong bean); Broad bean (fava); Chickpea (garbanzo); Guar; Jackbean; Lablab bean; Lentil; Pea (Pisum: includes dwarf pea, edible-podded pea, English pea, field pea, garden pea, green pea, snowpea, sugar snap pea); Pigeon pea; Soybean (immature seed); Sword bean. Dry varieties of Bean (Lupinus: includes grain lupin, sweet lupin, white lupin, white sweet lupin); Bean (Phaseolus: includes field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean, wax bean); Bean (Vigna: includes adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, yardlong bean);	3.75	1.55	6

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Broad bean (fava); Chickpea (garbanzo); Guar; Jackbean; Lablab bean; Soybean (immature seed); Sword bean Dry varieties of Lentil; Pea (Pisum: includes dwarf pea, edible-podded pea, English pea, garden pea, green pea, snowpea, sugar snap pea); Pigeon pea			
Leafy Vegetables: Amaranth (Chinese spinach); Arugula (roquette); Beet greens; Cardoon; Celery; Chinese celery; Celtuce; Chaya; Chervil; Edible-leaved chrysanthemum; Garland chrysanthemum; Corn salad; Cress (garden and upland); Dandelion; Dock (sorrel); Dokudami; Endive (escarole); Florence fennel; Gow kee; Lettuce (head and leaf); Orach, Parsley; Purslane (garden and winter); Radicchio (red chicory); Rhubarb; Spinach; New Zealand spinach; Vine spinach; Swiss chard; Watercress (upland); Water spinach	3.75	1.55	6
Herbs and Spices: Allspice, Angelica, Star anise, Annatto (seed), Balm, Basil, Corage, Burnet, camomile, Caper buds, Caraway, Black caraway, Cardamom, Cassia bark, Cassia buds, Catnip, Celery seed, Chervil (dried), Chive, Chinese chive, Cilantro (leaf), Cilantro (seed), Cinnamon, Clary, Clove buds, Coriander leaf (cilantro or Chinese parsley), Coriander seed (cilantro), Costmary, Cumin, Curry (leaf), Dill (dillweed), Dill (seed), Epazote, Fennel seed (common and Florence), Fenugreek, White ginger flower, Grains of paradise, Horehound, Hyssop, Juniper berry, Lavender, Lemongrass, Lovage (leaf and seed), Mace, Marigold, Marjoram (including oregano), Mexican oregano, Mioga flower, Mustard (seed), Nasturtium, Nutmeg, Parsley (dried), Pennyroyal, Pepper (black and white), Pepper leaves, Peppermint, Perilla, Poppy (seed), Rosemary, Rue, Saffron, Sage, Savory (summer and winter), Spearmint, Stevia levaes, Sweet bay, Tansy, Tarragon, Thyme, Vanilla, Wintergreen, Woodruff, Wormwood	3.75	1.55	6
Grass/Turfgrass/Sod Production	3.75	1.55	6
Grain Sorghum	3.75	1.55	6
Fruiting Vegetables: Eggplant; Groundcherry (Physalis spp); Pepino; Pepper (includes bell pepper, chili pepper, cooking pepper, pimento, sweet pepper); Tomatillo; Tomato	3.75	1.55	6
Forestry	8	8	8
Fallow	3.75	1.55	6
Cucurbits Vegetables/Fruit: Chayote (fruit); Chinese waxgourd (Chinese preserving melon); Citron melon; Cucumber; Gherkin; Edible gourd (includes hyotan, cucuzza, hechima, Chinese okra); Melons (all); Momordica spp (includes balsam apple, balsam pear, bittermelon, Chinese cucumber); Muskmelon (includes cantaloupe, casaba, crenshaw melon, golden pershaw melon, honeydew melon, honey ball melon, mango melon, Persian melon, pineapple melon, Santa Claus melon, snake melon); Pumpkin; Summer squash (includes crookneck squash, scallop squash, straightneck squash, vegetable marrow, zucchini); Winter squash (includes butternut squash, calabaza, hubbard squash, acorn squash, spaghetti squash); Watermelon	3.75	1.55	6

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Cotton	3.75	1.55	6
Corn (Field, Seed, Silage, Popcorn)	3.75	1.55	6
Conservation Reserve Program	3.75	1.55	6
Citrus Fruit Crop: All cultivars, varieties and/or hybrids of Calamondin; Chironja; Citron; Citrus hybrids; Grapefruit (including Japanese summer); Kumquat; Lemon; Lime (including Australian desert lime, Australian finger lime, Australian round lime, Brown river finger lime, Mount white, New Guinea wild, Russell river, sweet, and Tahiti); Mandarin (including Mediterranean and Satsuma); Orange (all); Pummelo; Tangelo; Tangerine (Mandarin); Tangor; Uniq Fruit (ugli)	3.75	1.55	8
Cereal and Grain Crop: barley, buckwheat, millet, oats, rye, quinoa, teff, teosinte, triticale, wild rice, rice, feed barley, wheat	3.75	1.55	6
Bulb Vegetables: All cultivars, varieties and/or hybrids of Chive (fresh leaves, including Chinese chive); Daylily (bulb); Elegans hosta; Fritillaria (bulb and leaves); Garlic (bulb, including great-headed and serpent garlic); Kurrant, Leek (including lady's and wild leek); Lily (bulb); Onion (including Beltsville bunching, bulb, Chinese bulb, fresh, green, macrostem, pearl, potato bulb, tree tops and Welsh onion tops); Shallot (bulb and fresh leaves)	3.75	1.55	6
Brassica Vegetable: Broccoli; Chinese broccoli (gai lon); Broccoli raab (rapini); Brussels sprouts; Cabbage; Chinese cabbage (bok choy); Chinese cabbage (napa); Chinese mustard cabbage (gai choy); Cauliflower; Cavalo broccoli; Collards; Kale; Kohlrabi; Mizuna; Mustard greens; Mustard spinach; Rape greens	3.75	1.55	6
Round-up Ready Flex Cotton	3.75	1.55	6
Round-up Ready Cotton	3.75	1.55	6
Round-up Ready Corn (GA-21)	3.75	1.55	6
Round-up Ready Corn 2 (NK603)	3.75	1.55	6
Round-up Ready Alfalfa	1.55	1.55	6
Round-up Ready Sugarbeets	3.75	1.55	6
Tropical/Subtropical Trees/Fruits: Ambarella; Atemoya; Avocado; Banana; Barbados cherry (acerola); Biriba; Blimbe; Breadfruit; Cacao (cocoa) bean; Canistel; Carambola (starfruit); Cherimoya; Coffee; Custard apple; Dates; Durian; Feijoa; Figs; Governor's plum; Guava; Ilama; Imbe; Imbu; Jaboticaba; Jackfruit; Longan; Lychee; Mamey apple; Mango; Mangosteen; Marmaladebox (genip); Mountain papaya; Noni (Indian mulberry); Papaya; Pawpaw; Plantain; Persimmon; Pomegranate; Pulasan; Rambutan; Rose apple;	3.75	1.55	8

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Sapodilla; Sapote (black, mamey, white); Spanish lime; Soursop; Star apple; Sugar apple; Surinam cherry; Tamarind; Tea; Ti (roots and leaves); Wax jambu			
Tree Nut Crops: Cultivars, varieties, and/or hybrids of African nut-tree; Almond; Beechnut; Brazil nut; Brazilian pine; Bunya; Burr oak; Butternut; Cajou nut; Candlenut; Cashew; Chestnut; Chinquapin; Coconut; Coquito nut; Dika nut; Ginkgo; Guiana chestnut; Hazelnut (Filbert); Heartnut; Hickory nut; Japanese horse-chestnut; Macadamia nut; Mongongo nut; Monkey-pot; Monkey puzzle nut; Okari nut; Pachira nut; Peach palm nut; Pecan; Pequi; Pili nut; Pine nut; Pistachio; Sapucaia nut; Tropical almond; Walnut (black, English); Yellowhorn	3.75	1.55	8
Sweet Corn	3.75	1.55	6
Sugar Cane	3.75	2.25	6
Stone Fruit: All cultivars, varieties and/or hybrids of Apricot; Cherry (sweet and tart); Nectarine; Olive; Peach; Plum/Prune (all types); Plumcot	3.75	1.55	8
Round-Up Ready Canola (Winter Varieties)	1.55	1.55	6
Soybeans	3.75	1.55	6
Sweet Corn with Round-Up Ready 2 Technology	3.75	1.55	6
Round-Up Ready Canola (Spring Varieties)	1.55	1.55	6
Vine Crops: grapes (raisin, table, wine), hops, passion fruit, kiwi	3.75	1.55	8

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Non Crop: Airports, airfields, apartment complexes, commercial sites, ditch banks, driveways, ramps, alleys, lanes, paths, trails, sidewalks, walkways, access roads, farm roads, highways (including aprons, medians, guardrails, and rights-of-way), paved areas and prior to paving, dry ditches, dry canals, fences and fencerows, golf courses, greenhouses, industrial sites, landscape areas, lumber yards, manufacturing sites, municipal sites, natural areas, office complexes, ornamentals, parks, campgrounds, sports areas, tennis courts, parking areas, cemeteries, petroleum or other tank farms and pumping installations, refineries, around telephone and communications equipment, public areas, drive-in theaters, railroads (including ballasts, shoulders, crossings and spot treatments), recreation areas, residential areas, rights-of-way, roadsides, firebreaks, schools, shadehouses, sports complexes, storage areas, substations, construction and pre-construction sites, turfgrass areas, around ornamental gardens, around ornamental trees and shrubs, power and utility sites, around commercial or industrial outbuildings, warehouse areas, bare ground, gravel yards, mulched areas, beaches, habitat restoration and management areas, uncropped farmstead areas, uncultivated non-agricultural areas, vacant lots, wastelands, shelter belts, and wildlife management areas. Natural Woodlands, including Wildlife and Habitat Management Areas, Wildlife Openings, Natural Areas (such as Wildlands and Wildlife Refuge), Campgrounds, Parks and Recreational Areas in Natural Forests, and Reforestation Treatments in Natural Forests	8	8	8
Aquatic	8	8	8
Alfalfa, Clover, and Other Forage Legumes, including: kudzu, lespedeza, lupin, sainfoin, trefoil, velvet bean, vetch, kenaf, leucaena	3.75	1.55	6
Berry and Small Fruit Crops: All cultivars, varieties and/or hybrids of Amur River grape; Aronia berry; Bayberry; Bearberry; Bilberry; Blackberry (including Andean blackberry, arctic blackberry, bingleberry, black satin berry, boysenberry, brombeere, California blackberry, Chesterberry, Cherokee blackberry, Cheyenne blackberry, common blackberry, coryberry, darrowberry, dewberry, Dirksen thornless berry, evergreen blackberry, Himalayaberry, hullberry, lavacaberry, loganberry, lowberry, Lucretiaberry, mammoth blackberry, marionberry, mora, mures deronce, nectarberry, Northern dewberry, olallieberry, Orgeon evergreen berry, phenomenalberry, rangeberry, ravenberry, rossberry, Shawnee blackberry, Southern dewberry, tayberry, youngberry, zarzamora); Blueberry (highbush and lowbush); Buffaloberry; Che; Chilean guava; Chokecherry; Cloudberry; Cranberry (including highbush); Currant (black, Buffalo, red, native); Elderberry; European barberry; Gooseberry; Grape; Honeysuckle (edible); Huckleberry; Jostaberry; Juneberry (Saskatoon berry); Kiwifruit (fuzzy and hardy); Ligonberry; Maypop; Mountain pepper berries; Mulberry; Muntries; Partridgeberry; Phalsa; Pincherry; Raspberry (black, red and wild); Riberry; Salal; Schisandra berry; Sea buckthorn; Serviceberry	3.75	1.55	8

Appendix D: Endangered Species Assessment

Consistent with EPA's responsibility under the Endangered Species Act (ESA), EPA intends to complete national-level endangered species Biological Evaluations for glyphosate to assess risks to federally threatened and endangered (listed) species from registered uses of pesticides. This Biological Evaluation will be completed in accordance with the joint Interim Approaches developed to implement the recommendations of the April 2013 National Academy of Sciences (NAS) report, *Assessing Risks to Endangered and Threatened Species from Pesticides*. The NAS report¹² outlines recommendations on specific scientific and technical issues related to the development of pesticide risk assessments that EPA and the Services must conduct to meet their obligations under the ESA. The methods developed as part of the joint Interim Approaches will continue to be vetted before EPA utilizes these methods broadly to meet its ESA obligations.

In November 2013, the U.S. Fish and Wildlife Service, the National Marine Fisheries Service (together, the Services), EPA, and the U.S. Department of Agriculture released a white paper containing a summary of their joint Interim Approaches for assessing risks to listed species from pesticides. These Interim Approaches were developed jointly by the agencies in response to the NAS recommendations, and reflect a common approach to risk assessment shared by the agencies as a way of addressing scientific differences between the EPA and the Services. Details of the joint Interim Approaches are contained in the November 1, 2013 white paper, *Interim Approaches for National-Level Pesticide Endangered Species Act Assessments Based on the Recommendations of the National Academy of Sciences April 2013 Report*.¹³

The ecological risk assessment supporting this Proposed Interim Registration Review for glyphosate does not contain a complete, national-level ESA analysis, including effects determinations for specific listed species or designated critical habitat. The agency intends to complete an assessment of risk to listed species prior to completing its final registration review decision for glyphosate. Final Biological Opinions for glyphosate will be developed by the Services. EPA intends to address risks to listed species identified in the Biological Opinions for glyphosate as part of its final registration review decision for glyphosate, and implement geographically-specific risk mitigation for listed species and designated critical habitats, as necessary, via *Bulletins Live! Two*. More information on *Bulletins Live! Two* is accessible at <https://www.epa.gov/endangered-species/bulletins-live-two-view-bulletins>.

¹² http://www.nap.edu/catalog.php?record_id=18344

¹³ <http://www.epa.gov/espp/2013/nas.html>

Appendix E: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, the EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, the EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for glyphosate, the EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA § 408(p), glyphosate is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

The EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where the EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, the EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The agency has reviewed all of the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. Glyphosate is on List 1 and the review conclusions are available in the glyphosate public docket (see EPA-HQ-OPP-2009-0361). A second list of chemicals identified for EDSP screening was published on June 14, 2013,¹⁴ and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit the EPA website.¹⁵ In this PID, the EPA is making no human health or environmental safety findings associated with the EDSP screening of glyphosate. Before completing this registration review, the agency will make an EDSP FFDCA § 408(p) determination.

¹⁴ See <http://www.regulations.gov#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074> for the final second list of chemicals.

¹⁵ <https://www.epa.gov/endocrine-disruption>

Exhibit 2

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



OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: April 23, 2018

SUBJECT: Glyphosate: Response to Comments on the Human Health Draft Risk Assessment

PC Code: 417300; 103601; 103603; 103604; 103605;
103607; 103608; 103613

Decision No.: 542736

Petition No.: NA

Risk Assessment Type: NA

TXR No.: NA

DP Barcode: D448021

Registration No.: NA

Regulatory Action: Registration Review

Case No.: 178

CAS No.: 1071-83-6; 38641-94-0; 70393-85-0;
114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7;
70901-12-1

40 CFR: § 180.364

MRID No.: NA

FROM: Monique M. Perron, Sc.D., Toxicologist
Tom Bloem, Chemist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

A handwritten signature in blue ink, reading "Monique Perron".

THROUGH: Christine L. Olinger, Branch Chief
RAB1/HED (7509P)

A handwritten signature in blue ink, reading "Christine L. Olinger".

TO: Khue Nguyen, Chemical Review Manager
Ricardo Jones, Team Leader
Amy Blankinship, Acting Branch Chief
Pesticide Re-evaluation Division (PRD; 7508P)

The Office of Pesticide Programs received thousands of public comments related to the human health draft risk assessment (DRA) for glyphosate in support of glyphosate's registration review. Comments addressing the human health risk assessment came from a wide array of stakeholders, including environmental non-governmental organizations (e.g., Natural Resource Defense Council, Center for Biological Diversity, Food & Water Watch, Environmental Working Group, Pesticide Action Network), consumer groups (e.g., Moms Across America, Environmental Action), pesticide registrants (e.g., the Joint Glyphosate Task Force, the Scotts Miracle-Gro Company), and private citizens (including anonymous commenters and growers). OPP has thoroughly reviewed all of the comments received during the public comment period. The Agency appreciates the substantial public interest in glyphosate. Due to the large volume of comments received on the risk assessment, the Agency identified the most detailed, substantive, and/or unique comments and addressed them as part of the identified "themes" below. Overall,

the comments received do not result in substantive changes to the Agency's human health risk assessment for glyphosate. EPA continues to conclude that exposure to glyphosate when used according to the label does not result in human health risk, including infants and children.

Cancer Assessment

- *Potential genotoxicity and carcinogenicity of glyphosate*
- *Consideration of Scientific Advisory Panel (SAP) recommendations*
- *Disagreement with International Agency for Research on Cancer (IARC) classification*
- *Weight of evidence evaluation of animal carcinogenicity data*

Several commenters expressed concern regarding the Agency's cancer assessment and disagreement with the Agency's cancer classification. Many of the commenters cited the IARC cancer classification of "probably carcinogenic to humans". The Agency conducted an independent evaluation of the cancer potential of glyphosate and concluded that glyphosate is "not likely to be carcinogenic to humans." This conclusion is based on a weight-of-evidence evaluation in accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment.

In December 2016, the Agency's evaluation of the human carcinogenic potential of glyphosate was presented to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) SAP for external peer review. This evaluation included an in-depth review of all relevant animal carcinogenicity and genotoxicity studies for the active ingredient glyphosate, as well as epidemiological studies that investigated potential carcinogenic effects from using pesticide products containing glyphosate. The epidemiological data was considered in this evaluation since it represents the best available data for evaluating human exposures and potential risk of cancer in the absence of epidemiological data on the active ingredient alone.

Although the panel did not reach complete consensus on several charge questions, none of the panel members believed glyphosate should be classified as "likely to be carcinogenic to humans" or "carcinogenic to humans". The Agency utilizes SAP reports as they represent the full continuum of opinions expressed. In the specific case of glyphosate, given the variety of opinions expressed, the Agency focused on statements where consensus appeared to be reached to revise the Issue Paper. The revised Issue Paper (D444689; TXR 0057688; G. Akerman; 12-DEC-2017) and a response to the SAP report (D444688; TXR 0057689; G. Akerman; 12-DEC-2017) along with associated supporting documents were released in December 2017¹.

Several public comments to the human health DRA were also received regarding the Agency's weight of evidence evaluation of the animal carcinogenicity data, including statistical evaluation, evaluation of preneoplastic and related non-neoplastic lesions, and use of historical controls. These comments have already been addressed in the response to the SAP report. Further information on the Agency's weight of evidence evaluation of the potential carcinogenicity of glyphosate can be found in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017).

¹ <https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate>

The Agency's conclusion that glyphosate is "not likely to be carcinogenic" is consistent with other countries and regulatory authorities/international organizations including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, European Food Safety Authority, the European Chemicals Agency, German Federal Institute for Occupational Safety and Health, The Joint FAO/WHO Meeting on Pesticide Residues, the New Zealand Environmental Protection Authority, and Food Safety Commission of Japan.

The Agency's analysis is more robust compared with IARC's evaluation. IARC considered a subset of the studies included in the Agency's evaluation. For instance, IARC only considered 8 animal carcinogenicity studies, while the Agency utilized 15 acceptable animal carcinogenicity studies in its evaluation. The Agency also did not use some studies that IARC incorporated into their evaluation because the studies were not appropriate for determining the human carcinogenic potential of glyphosate. For example, genotoxicity studies conducted in non-mammalian species (i.e., worms, fish, reptiles, plants) were excluded from the Agency's evaluation because they were not considered relevant for informing the genotoxic risk in humans. Furthermore, the Agency's process for evaluating the potential carcinogenicity of glyphosate is more transparent than IARC's process. As part of the SAP process, public participation is encouraged with the Agency's draft evaluation and all supporting documents provided in advance of the meeting, several opportunities available for oral and written public comments to be submitted, and the meeting was open to the public and available by webcast. The SAP meeting is well-documented with publication of a full transcript of the meeting and a final report drafted by SAP panel members. Additionally, the Agency drafted a response to the SAP report, which addressed the panel recommendations and identified revisions that were made in the Agency's Issue Paper following the SAP meeting. In contrast, IARC meetings are not accessible to the public. The committee deliberations are closed and the process does not allow for public comments to be submitted for consideration. Furthermore, there are no materials available in advance of the meeting, reports are final without any external peer review, and conclusions are not well described.

Glyphosate toxicological studies

- *Use and availability of industry generated studies*
- *The Agency should conduct search of open literature studies*
- *Chronic, developmental, reproductive, dermal, inhalation, neurotoxic, immunotoxic, and ocular effects*

Several commenters assert that the Agency relies too heavily on industry-funded studies and that these studies are not accessible to the public and requested the Agency to use open literature studies for the glyphosate hazard evaluation.

In the case of glyphosate, the Agency is aware of a significant number of studies published in the open literature. In 2012, the Office of Pesticide Programs (OPP) published a guidance document to provide guidance procedures for considering and using open literature toxicity studies to support human health risk assessment². This guidance assists OPP scientists in their judgement of the scientific quality of open literature publications and has been applied in the glyphosate

² U.S. EPA (2012). *Guidance for considering and using open literature toxicity studies to support human health risk assessment*. <http://www.epa.gov/pesticides/science/lit-studies.pdf>

review. More recently, the National Academy of Sciences National Research Council (NRC) has encouraged the Agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making³. The NRC defines systematic review as “a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies”⁴.

As part of the glyphosate registration review process, the Agency reviewed the open literature for hazard identification and characterization purposes in order to identify studies that could potentially impact the human health risk assessment. The first search was performed in late 2011/early 2012 and another search was performed in October 2015 using the concepts consistent with systematic review, such as detailed tracking of search terms and which literature have been included or excluded. The Agency also considered studies that were submitted by non-profit groups or members of the public as part of this 2015 review. These reviews are summarized in the DRA and a separate memo (D417703; TXR 0056885; M. Perron; 12-DEC-2017). Only a limited number of studies were deemed acceptable and appropriate for consideration in risk assessment. None of the studies were found to have an impact on the hazard characterization or draft human health risk assessment for glyphosate.

A fit-for-purpose systematic review was also executed to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate and reviewed by the SAP in 2016. This additional review identified numerous epidemiological and genotoxicity studies from the literature in addition to the guideline genotoxicity and animal carcinogenicity studies submitted to the Agency. Details regarding this review can be found in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017).

Under FIFRA, the Agency requires substantial amounts of toxicology and exposure data to be collected and submitted for pesticide registration. These studies, defined under the Title 40 Code of Federal Regulations (40 CFR) Part 158 Toxicology Data Requirements, provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and lifestyles. In general, many of these studies are commissioned and submitted by the pesticide producers. To ensure data quality and consistency, the Agency has standard guidelines for how testing is to be conducted. The Agency’s test guidelines are largely harmonized with those established by the Organisation for Economic Co-operation and Development (OECD). Harmonization also eases comparisons across studies and chemicals. Laboratories must also conduct studies in accordance with Good Laboratory Practices (GLP) standards (40 CFR Part 160) to further ensure the quality and integrity of the data submitted to the Agency. Study reports must include a statement on whether they were conducted in accordance with the GLP procedures. The Agency’s Office of Enforcement and Compliance Assurance (OECA) periodically inspects labs that conduct studies to support pesticide registrations to ensure they are in compliance with GLPs.

³ NRC 2011. “Review of the Environmental Protection Agency’s Draft IRIS Assessment of Formaldehyde”; NRC 2014. “Review of EPA’s Integrated Risk Information System (IRIS) Process”

⁴ NRC (2014). Review of EPA’s Integrated Risk Information System (IRIS) process. Washington, DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=18764

Review of all studies submitted to the Agency's Office of Pesticide Programs (OPP) is a multi-step process. Test reports must summarize and supply all the individual data obtained as part of the study; most toxicity study reports are well over a thousand pages long. An independent evaluation is prepared for each study and a Data Evaluation Record (DER) is generated to summarize the study methods, results, and conclusions. Draft DERs are subject to an internal peer review process, including review by multiple individual scientists and scientific review committees within OPP, to ensure accuracy and consistency with Agency guidance on interpretation of toxicity studies prior to finalization.

Studies evaluated by the Agency are available to the public through Freedom of Information Act (FOIA) requests, however, section 10(g) of FIFRA prohibits the Agency from disclosing certain information submitted by an applicant or registrant to any representative of a multinational pesticide producer or anybody who intends to deliver such information to a multinational pesticide producer. In order to receive registrant submitted data/studies, Section 10(g) requires requestors to sign an Affirmation of Non-Multinational Status form⁵. The form affirms the person requesting the pesticide data does not work for or represent a pesticide producer. Section 10(g) also requires the Agency to notify the data owner to whom we released the data to. Please keep in mind that registrant-submitted studies are proprietary and cannot be posted or released for public access. For more information on how to submit FOIA requests to access certain glyphosate studies, visit the Agency's website: <https://www.epa.gov/foia/foia-request-process>.

The entire toxicity database available is used to identify and characterize the potential health effects of a pesticide. This includes acceptable studies submitted by registrants and open literature studies. Although numerous comments were received regarding concerns for a suite of non-cancer effects, including chronic toxicity, ocular effects, developmental toxicity, reproductive toxicity, dermal effects, inhalation effects, neurotoxicity, and immunotoxicity, the available studies indicate that glyphosate will not elicit these effects, or these effects would only be observed at relatively high doses. Numerous studies are available that evaluated chronic exposure to glyphosate in rats, mice, and dogs. In most instances, effects were only seen at or near the limit dose (1000 mg/kg/day). Developmental effects in rats were only observed at a dose exceeding the limit dose (3500 mg/kg/day) and there were no developmental effects observed in rabbits. Route-specific studies are available that evaluated dermal and inhalation exposures. Dermal irritation effects were only seen at a dose exceeding the limit dose (5000 mg/kg/day), which is well above exposures expected from glyphosate use and not relevant for human health risk assessment. There were no effects observed in the inhalation study up to a dose approaching the limit concentration (0.36 mg/L). There was no evidence in the toxicological databases that glyphosate would cause ocular effects, reproductive effects, neurotoxicity, or immunotoxicity, including the guideline neurotoxicity battery, reproductive toxicity and immunotoxicity studies. Overall, the selected endpoints for risk assessment are protective of all adverse effects observed in the database.

Endocrine disruption

Some commenters assert that glyphosate is an endocrine disruptor based on open literature studies conducted primarily with commercial formulations containing glyphosate. For the few

⁵ <http://www2.epa.gov/foia/affirmation-non-multinational-status>

studies that evaluated glyphosate alone, there were no clear endocrine-related effects observed. Glyphosate was screened under the Agency's Endocrine Disruptor Screening Program (EDSP). Under the program, a suite of Tier 1 *in vivo* and *in vitro* studies was required for glyphosate that were designed to provide the necessary empirical data to evaluate the potential of glyphosate to interact with the estrogen, androgen, or thyroid signaling pathways. In addition to the available Tier 1 assay data, other scientifically relevant information, including general toxicity data and open literature studies of sufficient quality, are considered in the Agency's weight of evidence assessment. Based on all available information, the Agency concluded using a weight of evidence approach that the existing data do not indicate that glyphosate has the potential to interact with the estrogen, androgen, or thyroid signaling pathways (TXR 0057175; G. Akerman; 29-JUN-2015)⁶.

Protection of children

Several commenters assert that the Agency is not being protective of children. The Agency places top priority on the safety of children exposed to pesticides in food and/or water and living in or near areas treated with pesticides. The Food Quality Protection Act (FQPA) requires the Agency to give specific consideration to the potential for infants and children to be sensitive to pesticides⁷. Based on the 40 CFR Part 158 data requirements, pesticides typically have toxicology studies to evaluate effects in pregnant animals and their fetuses and young rats up through adulthood. Developmental and multi-generation reproduction studies are used to evaluate the potential effects of a pesticide on fetuses and offspring. Developmental studies are used to determine whether gestational exposure has an effect on the developing fetus. Multi-generation reproduction studies are used to evaluate parental and offspring toxicity, as well as reproductive toxicity, from long-term exposure to a pesticide. This includes exposure during gestation and lactation. The results of these studies are considered as part of the entire toxicity database to ensure doses selected for risk assessment are protective of any potential fetal and offspring effects.

Typical food-use pesticides have two developmental toxicity studies (one with rats and one with rabbits) and one study evaluating reproductive toxicity. In the case of glyphosate, there are 2 rat developmental, 2 rabbit developmental, and 3 reproductive toxicity studies available. The Agency found no indication that offspring are more sensitive to glyphosate from *in utero* or post-natal exposure in any of these studies. Additionally, any developmental or offspring effects were seen at doses much higher than those used for risk assessment. As part of the human health DRA to support registration review, the Agency evaluates all populations, including infants, children, and women of child-bearing age. There were no risks of concern identified for children from ingesting food/feed commodities or from entering/playing on residential areas treated with glyphosate using conservative assumptions to calculate high-end exposure estimates. Furthermore, in accordance with FQPA, aggregate exposures and risks from food, drinking

6 Available at <https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and>

7 HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (<https://www.epa.gov/children/epas-policy-evaluating-risk-children>).

water, and residential exposures were calculated for adults and children. There were no aggregate risks of concern. The Agency's current risk assessment is protective of children.

Detection of glyphosate in human milk, tissues, and urine

Many commenters cite reports of glyphosate detections in human milk, tissues, and urine. The Agency has identified several issues with studies claiming to detect glyphosate in urine, tissues, and human milk. Among the key information missing from such studies are the information related to sampling methods, sample storage, sample shipping, quality assurance and quality control, and analytical methods used, which are critical to evaluating the reliability of the data. Additionally, the enzyme-linked immunosorbent assay (ELISA) method is often used in the tests. This method is known to work well with surface waters that have little or no suspended solids or with processed drinking water. However, many of the samples in these cited tests would have significant amounts of dissolved solids which may lead to issues when using the ELISA method with these sample types. Furthermore, the ELISA method is generally considered to be a semi-quantitative method that is typically used as a screening or initial test method to determine the potential presence of a chemical. The results from such a method, therefore, do not provide data that can be used quantitatively for human health risk assessment.

Glyphosate is not expected to accumulate in human milk and tissues. The Agency is not aware of any peer-reviewed studies reporting detection of glyphosate in human breast milk and, due to its physicochemical properties, glyphosate is not expected to bioaccumulate in the human body. Additionally, as noted in the DRA, the Agency Biological and Economic Analysis Division (BEAD) analyzed human milk samples in response to concern from segments of the general public related to the presence of glyphosate in human milk. Glyphosate, *N*-acetyl-glyphosate, and aminomethyl phosphonic acid (AMPA) were not detected in any of the human milk samples. On the other hand, detection of trace amounts of glyphosate in urine would be expected given the chemical does not bioaccumulate and is primarily excreted un-metabolized as glyphosate by mammals. Such trace levels of glyphosate are not of concern to the Agency since the corresponding body burden (or approximate magnitude of exposure in mg/kg body weight) assuming complete excretion of the absorbed amount and virtually no metabolism, would still be well below current regulatory levels⁸.

Formulations:

- *Toxicity of inert compounds*
- *Transparency of components*
- *Contaminants in pesticide products*

Several commenters expressed concern that glyphosate formulations are more toxic than glyphosate alone and question the toxicity of inert ingredients, the lack of transparency around other ingredients in product formulations, and other contaminants in pesticide products. Most pesticide products contain substances in addition to the active ingredient(s) that are often referred to as inert or other ingredients, which aid in the performance and effectiveness of the pesticidal

⁸ Niemann et al. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. *Journal of Consumer Protection and Food Safety*. 10: 3-12.

product. Federal law does not require that these ingredients be identified by name or percentage on the label. In accordance with FIFRA, the Agency cannot disclose this information since these ingredients are considered trade secrets or confidential business information.

All active and inert pesticide ingredients must be approved for use by the Agency. The Agency carefully evaluates the active and inert components hazard potential (i.e., toxicity) of a pesticide product with a battery of appropriate toxicity data. However, there are tens of thousands of different registered pesticide products available in the marketplace and, though the Agency evaluates the product components, long term testing of individual products is not required. Any contaminants or impurities associated with formulation components need to be reported to the Agency and are evaluated on a case by case basis. The Agency looks at the amount of the impurity in the formulation, the manufacturing information, and what steps are taken to limit or remove impurities. A comment was received regarding formation of nitrosamines, which have been found to cause cancer. Technical grade glyphosate contains minor amounts of a nitrosamine impurity, N-nitrosoglyphosate (NNG). This contaminant was considered previously as part of the Reregistration Eligibility Decision (RED)⁹. Carcinogenicity testing of nitroso contaminants is normally required only in cases which the level of nitroso compounds exceeds 1.0 ppm. Analyses showed that greater than 92% of the individual technical glyphosate samples contained less than 1.0 ppm. No new data have been presented to warrant a reevaluation of the Agency's conclusion that the NNG content of glyphosate is not toxicologically significant.

Glyphosate has been studied in a multitude of studies and there are studies that have been conducted on numerous formulations that contain glyphosate; however, there are relatively few research projects that have attempted to directly compare glyphosate to the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations. The majority of studies using commercial formulations identified as part of the systematic review are *in vitro* studies, which are difficult to translate into *in vivo* effects where metabolism and clearance would play a large role in potential toxicity.

Consequently, *in vivo* studies are given more weight. In the systematic review (D417703; TXR 0056885; M. Perron; 12-DEC-2017), none of the *in vivo* studies with commercial formulations were found to be of adequate quality for use in human health risk assessment. Common limitations/deficiencies seen in these studies included lack of test material information, exposure conditions were not adequately described or documented, data were only presented as graphs and often measures of variability were not included, samples sizes were too small for the type of study conducted and/or not reported for all lifestages, only one dose was tested, and age and overall health prior to commencing a study was not reported. Furthermore, most of these studies focused on clinical chemistry measurements (i.e., enzymes, hormones, electrolytes) or histopathological examinations (without reporting severity) making it difficult to determine the adversity of the results. The relationship between any changes noted in these effects and possible adverse apical outcomes from commercial formulations has not been established. As described in the NRC report, "Toxicity Testing in the 21st Century"¹⁰, to develop a mode of action/adverse outcome pathway (MOA/AOP) not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established. In

⁹ https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf

¹⁰ National Research Council (NRC). 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, D.C. The National Academies Press.

other words, how much of a change in one key event is needed to result in an adverse effect at the next level of biological organization? Thus, certain exposures to a chemical may impact normal physiological responses in a way that may not necessarily be adverse, and thus, the MOA/AOP concept requires an understanding of adaptive/homeostatic capacity of biological systems and their limits, relative to concentration and duration of exposure. Without an MOA/AOP understanding or even a potentially solid hypothesis, perturbations in physiology cannot be interpreted for risk assessment without understanding how these changes lead to adverse outcomes.

The Agency has been collaborating with the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences to develop a research plan intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity. The results of this research will be considered when available.

Antibacterial properties and disruption of the gut microbiome

Many commenters assert that glyphosate has antibacterial properties and claim it contributes to antibiotic resistance and disruption of the gut microbiome. The metabolic pathway inhibited in plants by glyphosate (Shikimate pathway) is also found in many microorganisms. Although glyphosate may inhibit the Shikimate pathway in microorganisms, it has not been demonstrated to be an effective antimicrobial for treating humans. It is particularly difficult to achieve and maintain a sufficiently high concentration of glyphosate in the body to be an effective antimicrobial agent due to the low absorption and metabolism of glyphosate. Furthermore, although glyphosate may inhibit the production of certain amino acids in bacteria, these amino acids can be acquired from the body, when needed. Therefore, the inhibition does not necessarily lead to bacterial death.

Gut microbiomes (colonies of microbes in the gut) are unlikely to be altered from glyphosate exposure since the aromatic amino acids produced via the Shikimate pathway are also available in the human gut via the diet since humans are unable to synthesize them. Therefore, despite inhibition of this metabolic pathway, the microorganisms are still capable of growing and surviving. It has been suggested that glyphosate preferentially affects only “good” bacteria; however, this implies that microbes are defined by this metabolic pathway, which is not scientifically supported. Gut microbiomes are not evaluated directly in guideline toxicity studies; however, the stomach and gastrointestinal tract are routinely examined in several studies by gross evaluation and histopathological investigations. There are no indications in these studies that exposure to glyphosate induces adverse effects in those organs.

Metal chelation and nutritional deficiencies

Some commenters indicated that glyphosate is a metal chelator and consequently claim that it causes nutritional deficiencies. Glyphosate chelates with some metals in soil and aquatic environments. The relative proportion of the various chemical species of glyphosate (including dissociated species of glyphosate acid and glyphosate-metal complexes) is dependent on chemical characteristics (*e.g.*, pH, redox potential, etc.) of the environment. The Agency is unaware of any connection between metal chelation and toxicity of glyphosate in mammals. In

guideline studies for human health, exposure to glyphosate did not result in any changes in clinical or blood chemistry measurements, suggesting that glyphosate-metal chelation does not play a significant role in affecting human health.

Dietary Assessment

- *Residues in food and beverages*
- *Assessment of the dessicant use on wheat*

Many commenters point to reports of glyphosate residues being detected in food/beverage commodities such as honey, cereals, wine, and orange juice and expressed concerns about consumer safety. Due to its widespread use, trace amounts of glyphosate residues may be found in various food and beverage commodities. However, these trace amounts are not of concern to the consumer as the residue levels are well below tolerance levels established in/on food commodities treated with glyphosate. For example, the Agency has received information on glyphosate residues reported in orange juice at a maximum of 26 ppb. At this concentration, a 10 kg child would have to consume approximately 385 liters (1627 servings of an 8 oz glass) of orange juice every day to reach the chronic reference dose of 1 mg/kg/day.

As part of the human health risk assessment, the Agency evaluated dietary exposure to glyphosate for all populations, including infants, children, and women of child-bearing age. There were no dietary risks of concern for glyphosate using an unrefined analysis, which assumes all food commodities contain tolerance level residues (i.e., maximum legal residues allowed on a food commodity) of glyphosate, all food (with registered uses) has been treated with glyphosate, and using high-end estimates of glyphosate in drinking water.

Other commenters pointed to the use of glyphosate as a pre-harvest desiccant for wheat as a source of glyphosate residues in cereal products. Since the dietary exposure assessment was unrefined (assumed tolerance level residues and 100% crop treated) and the current tolerances reflect all registered uses, the wheat desiccant use was considered in the dietary analysis conducted as part of the human health DRA for registration review and there were no dietary risks of concern.

Non-Cancer Diseases

Several commenters expressed concern about the alleged link between exposure to glyphosate and various non-cancer diseases. In several instances, commenters noted a correlation in glyphosate use and some diseases; however, correlation does not imply causation. Increased prevalence of a disease may be due to many possible causes and verifying these causes should not be based on speculation. Determining whether an observed association represents a cause-effect relationship between glyphosate exposure and disease requires additional consideration of criteria, such as the modified Bradford-Hill criteria, that evaluate strength, consistency, dose response, temporal concordance and biological plausibility across multiple lines of evidence. Additionally, the plant MOA/AOP is not relevant for mammalian systems and there is a distinct lack of mechanistic understanding for the toxicity of glyphosate in mammals, which is used to inform the cause-effect relationship. As part of the Tier II Incident Report for glyphosate

(D417808; S. Recore; 6-FEB-2014;), an open literature search was conducted to identify epidemiological studies that evaluated the potential role of glyphosate and disease outcomes. The Agency reviewed studies related to a range of non-cancer effects, including adverse birth outcomes, respiratory effects, rheumatoid arthritis, diabetes, myocardial infarction, Parkinson's disease, and retinal degeneration. Most of the studies were not designed to develop data on non-cancer outcomes that could be used quantitatively or qualitatively in regulatory decision-making, but were more exploratory in nature. Additionally, in most instances, only one study was available for a specific outcome, which makes it challenging to assess consistency in the human population. Based on the available studies, the Agency could not conclude that glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. The Agency also examined journal articles regarding non-cancer disease outcomes submitted with comments to the DRA to identify any epidemiological studies that were not considered as part of the Tier II report. At this time, the available scientific data do not support a cause-and-effect relationship between exposure to glyphosate and any non-cancer disease outcomes. The Agency will continue to follow the epidemiological literature concerning the potential role of glyphosate in certain non-cancer health outcomes.

Exhibit 3

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



OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: January 13, 2019

SUBJECT: Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment

PC Code: 417300; 103601; 103603; 103604; 103605;
103607; 103608; 103613

Decision No.: 558081

Petition No.: NA

Risk Assessment Type: NA

TXR No.: NA

DP Barcode: D455459

Registration No.: NA

Regulatory Action: Registration Review

Case No.: 178

CAS No.: 1071-83-6; 38641-94-0; 70393-85-0;
114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7;
70901-12-1

40 CFR: §180.364

MRID No.: NA

FROM: Monique M. Perron, Sc.D., Toxicologist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

A handwritten signature in blue ink, reading "Monique Perron".

THROUGH: Christine L. Olinger, Branch Chief
RAB1/HED (7509P)

A handwritten signature in blue ink, reading "Christine L. Olinger".

TO: Steven Peterson, Chemical Review Manager
Dana Friedman, Branch Chief
Pesticide Re-evaluation Division (PRD; 7508P)

The Office of Pesticide Programs received hundreds of thousands of public comments on the proposed interim decision (PID) for glyphosate as part of registration review. Comments regarding the human health risk assessment came from a wide array of stakeholders. Topics relating to human health included concerns with the agency's cancer assessment, toxicological studies, protection of children, and detections of glyphosate. These comments regarding the human health risk assessment for glyphosate have been previously addressed in the *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* (D448021; M. Perron; 23-APR-2018) and did not result in changes to the agency's risk assessment.

During the public comment period, 65 open literature studies were also identified for the agency's consideration (Appendix A). Of these, 23 were previously identified and considered by

the agency as part of two open literature searches conducted to support the draft human health risk assessment for registration review. The agency reviewed the open literature as part of the *Glyphosate Systematic Review of Open Literature* (D417703; TXR 0056885; M. Perron; 12-DEC-2017) for hazard identification and characterization purposes in order to identify studies that could potentially impact the human health risk assessment. A fit-for-purpose systematic review was also executed to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate and detailed in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017).

The remaining 42 studies identified during the public comment period were primarily journal articles published since these searches were conducted. The majority of the studies did not warrant detailed evaluation for a variety of reasons, such as no effects seen from glyphosate exposure, administration via a non-relevant route, effects seen at doses higher than the current points of departure, only one dose was tested eliminating the potential for dose-response evaluation, lack of glyphosate measurements, and exposure or biomonitoring studies that would not impact risk estimates. Furthermore, several studies were conducted *in vitro* or evaluated biochemical or molecular effects that are difficult to translate into *in vivo* effects. These studies are typically considered as part of mode of action/adverse outcome pathway (MOA/AOP) analyses. As a result, *in vivo* studies are given more weight at this time.

For the *in vivo* studies identified, the most common limitations/deficiencies were related to the nature of the test substance(s) used for exposure. Many of the studies used commercial formulations or dilutions; however, direct measurements of the active ingredient were not conducted in order to determine actual dose concentrations and/or identification information was not provided for the formulation used. There are numerous glyphosate formulations and providing a general product name, such as Roundup, does not provide the agency with information to ascertain the exact formulation used and determine all of its chemical components. Additionally, several studies were conducted in other countries and utilized formulations that are not registered in the United States. As a result, the active ingredients and other components of the formulation are unknown, and any potential effects cannot be attributed to glyphosate and/or defined glyphosate concentrations.

Several *in vitro* genotoxicity studies were identified for consideration. Although positive results were observed in some of these studies, there would be no impact on the agency's weight of evidence evaluation of the genotoxic potential of glyphosate since there is sufficient evidence in the existing database (described in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*; D444689; TXR 0057688; G. Akerman; 12-DEC-2017) to conclude that the *in vitro* effects claimed by the study authors do not lead to genotoxicity *in vivo*.

Two additional journal articles on the association between glyphosate exposure and non-Hodgkin lymphoma (NHL) were identified for detailed review (D455531; D. Miller; 6-JAN-2020;). The following are brief summaries of these journal articles and the agency's reviews:

- Zhang et al. (2019) is a review article summarizing epidemiological studies between 2001 and 2018 on the association between glyphosate exposure and NHL. All of the data/information included in the article was previously considered by the agency as part

of the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017); however, the authors conducted their own meta-analysis to incorporate recently published risk estimates for the Agricultural Health Study (AHS) cohort (Andreotti et al., 2018) based on their *a priori* hypothesis that the highest exposures to glyphosate will lead to increased risk of NHL in humans¹. In its detailed review of this study, the agency identified concerns with the meta-analysis as performed by the authors. A supplemental analysis by the agency indicated that a lower non-statistically significant meta-risk ratio of 1.14 (95% CI: 0.87-1.50) would be obtained if the Andreotti et al. (2018) study is properly incorporated into the meta-analysis². Therefore, the meta-analyses performed by Zhang et al. (2019) would not impact the conclusions presented in the agency's revised issue paper.

- Leon et al. (2019) is a pooled analysis of NHL in agricultural cohorts from France, Norway, and the United States (the AHS cohort). For overall NHL malignancies and NHL subtypes, except diffuse large B-cell lymphoma (DLBCL), glyphosate risk estimates were less than 1. For DLBCL a somewhat elevated, but non-statistically significant risk estimate of 1.36 (95% CI: 1.00-1.85) was observed. While the analysis benefited from a combined cohort of more than 300,000 farmers and farmworkers from different countries, only the cohort from the United States used actual measurement instruments (self-administered questionnaire) for glyphosate exposure where a smaller risk estimate for the DLBCL subtype of 1.2 (95% CI: 0.72-1.98) was obtained. Furthermore, the nature and characteristics of the three cohorts differed in substantive ways and it is not clear that the statistical adjustments made were adequate to account for these differences.

Therefore, none of the open literature studies identified for the agency's consideration were found to have an impact on the glyphosate hazard characterization, cancer assessment, or human health risk assessment. The agency will continue to monitor the open literature for studies that use scientifically sound and appropriate methodology and relevant routes of exposure that have the potential to impact the risk evaluation of glyphosate.

¹ Here, higher exposures correspond to higher levels, longer durations, and/or greater lags/longer latencies.

² We note, however, that the meta-estimate in our Revised Glyphosate Issue paper was 1.27 (95% CI: 1.01, 1.59) while our updated estimate after incorporating the Andreotti et al. (2018) paper is 1.14 (95% CI: 0.87, 1.50). See D. Miller; D455531; 6-JAN-2020 for details and information.

Appendix A. Studies identified for the agency's consideration during the public comment period for the Proposed Interim Decision (PID).

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Aiassa, D	2019	Evaluation of genetic damage in pesticide applicators from the province of Cordoba, Argentina	No	ecological epidemiological study; no glyphosate-specific estimates; would be assigned low quality ranking according to process detailed in revised issue paper on evaluation of carcinogenic potential
Alvarez-Moya, C	2013	Comparison of the <i>in vivo</i> and <i>in vitro</i> genotoxicity of glyphosate isopropylamine salt in three different organisms	Yes	--
Astiz, M	2009	Antioxidant defense system in rats simultaneously intoxicated with agrochemicals	Yes	--
Baier, Carlos J	2017	Behavioral impairments following repeated intranasal glyphosate-based herbicide administration in mice	No	Argentina formulation; micropipette administration into nostrils (not a relevant route); one dose tested; no glyphosate measurements
Benbrook, CM	2019	How did US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?	No	review paper; examined list of studies published since agency's evaluation; supplemental tables comparing EPA and IARC yielded one study to reexamine (Gasnier et al. 2009 included in table below)
Bolognesi, C	2009	Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate	Yes	--
Bolognesi, C	1997	Genotoxic Activity of Glyphosate and Its Technical Formulation Roundup	Yes	--

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Bolognesi, C	2011	Micronuclei and pesticide exposure	No	Review article for biomonitoring studies for several pesticides; already considered the one study on glyphosate (Bolognesi et al. 2009) in previous systematic review
Brendler-Schwaab, S	2005	The <i>in vivo</i> comet assay: use and status in genotoxicity testing	No	No glyphosate information
Caballero, M	2018	Estimated Residential exposure of agricultural chemicals and premature mortality by Parkinson's disease in Washington state	No	Glyphosate exposure assessed indirectly using geospatial information on residential address and crop data from WA State from 2011-2015; residential address was based only on address listed in the death registry for 2011-2015 so the analysis was cross-sectional in nature and was unable to assess potential lifetime exposure based on either changes in WA State agriculture or changes in residential address; statistical analysis only considered the demographic variables sex, race, marital status, and education indicating limited ability to assess confounding or control for co-exposure to pesticides and other environmental factors; given these limitations, the modest risk estimate of 1.3 (95% CI: 1.0-1.62) may reflect residual confounding and is based on a low quality exposure assessment that did not directly assess individual exposure or allow the investigators to assess lifetime exposure

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Cavalli, VL	2013	Roundup disrupts male reproductive functions by triggering calcium-mediated cell death in rat testis and Sertoli cells	Yes	--
Dimitroy, BD	2006	Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems	Yes	--
Gasnier, C	2009	Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines.	Yes	In previous open literature review considered non-relevant; reexamination indicated it is relevant; in vitro study evaluating glyphosate alone and formulations for cytotoxicity, estrogenic activity, anti-androgenic activity and aromatase disruption; only effect reported for glyphosate alone was a statistically significant, non-concentration dependent increase in anti-androgenic activity
Gehin, A	2005	Vitamins C and E reverse effect of herbicide-induced toxicity on human epidermal cells HaCat: a biochemometric approach	Yes	--
Ghisi, N	2016	Does exposure to glyphosate lead to an increase in the micronuclei frequency? A systematic and meta-analytic review	Yes	--
Gillezeau, C	2019	The evidence of human exposure to glyphosate: a review	No	Exposure study; review article; no impact on risk estimates
Grisolia, C	2002	A comparison between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides	Yes	--
Heu, C	2012	Glyphosate-induced stiffening of HaCaT keratinocytes, a Peak Force Tapping study on living cells	Yes	--

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Jiang, Xiao	2018	A commercial Roundup formulation induced male germ cell apoptosis by promoting the expression of XAF1 in adult mice.	No	Formulation by gavage at 60, 180 or 540 mg/kg/day and in vitro exposures; no glyphosate measurements; potential effects only seen at dose higher than current POD
Kasuba, V	2017	Effects of low doses of glyphosate on DNA damage, cell proliferation and oxidative stress in the HepG2 cell line	No	In vitro study evaluating DNA damage, cell proliferation and oxidative stress in HepG2 cells tested at 3 concentrations of glyphosate; non-statistically significant increase in proliferative response; primary DNA damage (comet assay) decreased relative to negative control; increase in MN and effects on lipid peroxidation were not concentration dependent; no convincing glyphosate-related effects
Kojima, H	2010	Endocrine-disrupting Potential of Pesticides via Receptors and Aryl Hydrocarbon Receptor	No	Mini-review; only mention of glyphosate is in one table and it was negative for all receptors
Kongtip, P	2017	Glyphosate, and paraquat in maternal and fetal serum in Thai Women	No	Exposure study; no impact on risk estimates
Kubsad, D	2019	Assessment of Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology	No	Intraperitoneal injection of glyphosate at 25 mg/kg/day in pregnant females; not a relevant route
Kwiatkowska, M	2016	DNA damage and methylation induced by glyphosate in human peripheral blood mononuclear cells (in vitro study)	No	Report primary DNA damage at high concentrations of glyphosate (0.5 mM and higher) and increase in DNA methylation of p53 and p16 promoters; methylation was statistically significantly increased at both concentrations for the p53 promoter, but not p16; not enough concentrations tested to make a conclusion on impact of glyphosate on p53 methylation.

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Leon, M	2019	Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium	No	Detailed review performed (D. Miller; 6-JAN-2020; D455531); summarized in text above
Lioi, M	1998	Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro	Yes	--
Lueken, A	2004	Synergistic DNA damage by oxidate stress (induced by H2O2) and nongenotoxic environmental chemicals in human fibroblasts	Yes	--
Manas, F	2009	Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetics test	Yes	--
Manas, F	2009	Genotoxicity of glyphosate by the comet assay and cytogenetic test	Yes	--
Manservigi, F	2019	The Ramazzini Institute 13- week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system	No	Glyphosate and formulation; no blinding to dose; small sample size for developmental evaluation (n=8/dose); generally no adverse effects observed; only one dose tested; no glyphosate measurement
Mao, Q	2018	The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome	No	Glyphosate and formulation; no glyphosate measurement; evaluated changes in microbiome; no link to adverse apical outcomes
Martinez, A	2019	Effects of glyphosate and aminomethylphosphonic acid on an isogenic model of the human blood-brain barrier	No	In vitro study; no glyphosate measurements
Mensah, PK	2015	Ecotoxicology of glyphosate and glyphosate-based herbicide - toxicity to wildlife and humans	No	Book chapter; all references on human health effects from glyphosate already considered

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Mesnage, R	2016	Multimomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide	No	Belgium formulation; proteome and metabolome data; changes may reflect adaptive liver effects; no link to adverse apical outcomes
Milesi, MM	2018	Perinatal exposure to a glyphosate-based herbicide impairs female reproductive outcomes and induces second-generation adverse effects in Wistar rats	No	Argentina formulation by diet at 2 or 200 mg/kg/day; potential effects at dose higher than current POD
Milic, M	2018	Oxidative stress, cholinesterase activity, and DNA damage in the liver, whole blood, and plasma of Wistar rats following a 28-day exposure to glyphosate	No	Glyphosate administered via gavage at 0.1, 0.5, 1.75, and 10 mg/kg/day; glyphosate was not measured in dose preparations and small sample size (n=5) used; no change in body and liver weights; plasma and liver ROS and plasma GSH levels similar to controls, no change in GSH activity in blood, inconsistent cholinesterase data and no neurotoxicity MOA/AOP for glyphosate
Mills, PJ	2019	Glyphosate excretion is associated with steatohepatitis and advanced liver fibrosis in patients with fatty liver disease	No	Study measured glyphosate/AMPA metabolite excretion levels in NAFLD patients who were either NASH (Non-Alcoholic Steatohepatitis) or not NASH patients and compared glyphosate and AMPA measurement in urine; no subjects without NAFLD; problems with temporality; single urine measurement only; no information collected on dietary intake or occupation
Mills, PJ	2017	Excretion of the herbicide Glyphosate in older adults between 1993-2016	No	Exposure/biomonitoring study; no impact on risk estimates
Niemann, L	2015	A critical review of glyphosate findings in human urine sample and comparison with the exposure of operators and consumers	No	Review article for exposure; no impact on risk estimates; calculations show glyphosate exposure well below

Author	Year	Title	Part of previous agency open literature reviews?	Comments
				acceptable daily intake (ADI) and acceptable operator exposure levels (AOEL)
Parvez, S	2018	Glyphosate exposure in pregnancy and shortened gestational length: a prospective Indiana birth cohort study	No	Glyphosate levels in urine and drinking water; cross-sectional study evaluating correlation; no AMPA metabolite measured; small sample size; limited diversity; no evaluation of other chemical exposures (except smoking, caffeine, and alcohol)
Panzacchi, S	2018	The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: study design and first in-life endpoints evaluation	No	Glyphosate and formulation; no glyphosate measurement; no adverse effects observed
Perry, M	2019	Historical evidence of glyphosate exposure from a US agricultural cohort	No	Exposure/biomonitoring; no impact on risk estimates
Pham, T	2019	Perinatal exposure to glyphosate and a glyphosate-based herbicide affect spermatogenesis in mice	No	Glyphosate and Belgium formulation; no glyphosate measurement; small sample size for some parameters; no adverse effect in several parameters; small magnitude of change and/or lack of dose response in others; no incidence or severity scores reported for histopathological evaluations
Portier, C	2016	Difference in the carcinogenic evaluation of glyphosate between the IARC and EFSA	Yes	--
Prasad, S	2009	Clastogenic Effects of Glyphosate in Bone Marrow Cells of Swiss Albino Mice	Yes	--
Richard, S	2005	Differential Effects of Glyphosate and Roundup on Human Placenta Cells and Aromatase	Yes	--

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Roustan, A	2014	Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation	Yes	--
Saleh, SM	2018	Hepato-morphology and biochemical studies on the liver of albino rats after exposure to glyphosate-Roundup	No	Egypt formulation; no glyphosate measurements; histopathological findings cannot be interpreted without incidence or severity scoring
Santovito, A	2018	In vitro evaluation of genomic damage induced by glyphosate on human lymphocytes	No	Authors report chromosomal aberrations and micronuclei formation in human lymphocytes treated in vitro with 0.025 µg/mL glyphosate and above; effects reported are inconsistent with other findings in the literature; sample size too small to make reliable conclusions for low test concentration
Schimpf, MG	2015	Neonatal exposure to a glyphosate based herbicide alters the development of the rat uterus	No	sc injection (not a relevant route); formulation not registered in US; no glyphosate measurements; only one dose tested
Sena de Souza, J	2019	Maternal glyphosate-based herbicide exposure alters antioxidant-related genes in the brain and serum metabolites of male rat offspring	No	Brazil formulation; gene expression profiles; no link to adverse apical outcomes
Sena de Souza, J	2017	Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats	No	Brazil formulation; no glyphosate measurements; no changes in T3 or T4; TSH decreased rather than increased and presented a flat dose response; hormone measurement calibration information not reported; gene and metabolomic data
Seneff, S	2018	Is Glyphosate a key factor in mesoamerican nephropathy?	No	Review article; hypothesis generating paper
Sivikova, K	2005	Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes	Yes	--

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Stur, E	2019	Glyphosate-based herbicides at low doses affect canonical pathways in estrogen positive and negative breast cancer cell lines	No	Brazil formulation testing with breast cancer cell lines; no glyphosate measurements
Szepanowksi, F	2018	Differential impact of pure glyphosate and glyphosate-based herbicide in a model of peripheral nervous system myelination	No	No differences in myelination in cultures treated with glyphosate compared to vehicle control
Teleken, JL	2019	Glyphosate-based herbicide exposure during pregnancy and lactation malprograms the male reproductive morphofunction in F1 offspring	No	Brazil formulation; no glyphosate measurements/only one dose tested that is above current POD
Thongprakaisang, S	2013	Glyphosate induces human breast cancer cells growth via estrogen receptors	Yes	--
Townsend, M	2017	Evaluation of various glyphosate concentrations on DNA damage in human Raji cells and its impact on cytotoxicity	No	DNA damage in vitro only at concentrations that the authors report as several orders of magnitude larger than those attainable in vivo
Vigfusson, N	1980	The effect of the pesticides, Dexon, Captan and Roundup, on sister-chromatid exchanges in human lymphocytes in vitro	Yes	--
Von Ehrenstein, O	2019	Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study	No	Assumed exposure from agricultural application records (no actual measurements) other exposure pathways not considered; addresses at time of enrollment may not reflect an individual's exposure over pregnancy
Walsh, L	2000	Roundup Inhibits Steroidogenesis by Disrupting Steroidogenic Acute Regulatory (StAR) Protein Expression	Yes	--
Wang, L	2019	Glyphosate induces benign monoclonal gammopathy and promotes multiple myeloma progression in mice	No	incorrect EPA chronic reference dose cited; only one dose tested that is above current POD

Author	Year	Title	Part of previous agency open literature reviews?	Comments
Wozniak, E	2018	The mechanism of DNA damage induced by Roundup 360 PLUS, glyphosate and AMPA in human peripheral blood mononuclear cells - genotoxic risk assessment (Accepted Manuscript)	No	In vitro study using human lymphocytes; DNA damage at glyphosate concentrations of 250 µM and higher
Zhang, L	2019	Exposure to glyphosphate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence	No	Detailed review performed (D. Miller; 6-JAN-2020; D455531); summarized in text above

Exhibit 4



Glyphosate

Interim Registration Review Decision
Case Number 0178

January 2020

Approved by: 
Elissa Reaves, Ph.D.
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Date: 1-22-2020

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I. INTRODUCTION

This document is the Environmental Protection Agency's (the EPA or the agency) *Interim Registration Review Decision* (ID) for glyphosate acid (PC Code 417300) and its various salt forms (PC Codes 103601, 103604, 103605, 103607, 103608, and 103613; case 0178), and is being issued pursuant to 40 CFR § 155.56 and 155.58. A registration review decision is the agency's determination whether a pesticide continues to meet, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The agency may issue, when it determines it to be appropriate, an Interim Registration Review Decision before completing registration review. Among other things, the Interim Registration Review Decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review case. Additional information on glyphosate can be found in the EPA's public docket (EPA-HQ-OPP-2009-0361) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by the EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at <http://www2.epa.gov/pesticide-reevaluation>. In 2006, the agency implemented the registration review program pursuant to FIFRA § 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

The EPA is issuing an ID for glyphosate so that it can (1) move forward with aspects of the registration review case that are complete and (2) implement interim risk mitigation (see Appendices A and B). The agency is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (collectively referred to as, the Services) to develop methodologies for conducting national threatened and endangered (listed) species assessments for pesticides in accordance with the Endangered Species Act (ESA) § 7. Therefore, although the EPA has not yet fully evaluated risks to federally-listed species, the agency will complete its listed species assessment and any necessary consultation with the Services for glyphosate prior to completing the glyphosate registration review. Likewise, the agency will complete endocrine screening for glyphosate, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), before completing registration review. See Appendices D and E, respectively, for additional information on the listed species assessment and the endocrine screening for the glyphosate registration review.

In addition, in September 2018, the Environmental Working Group (EWG) along with several other stakeholders, collectively referred to as EWG et al. hereafter, petitioned the agency to

reduce the glyphosate tolerance in oats to 0.1 parts per million (ppm) and to require labels for registered glyphosate products to explicitly prohibit the use of glyphosate as a preharvest desiccant. The agency is in the process of reviewing comments submitted on the 2018 EWG et al. petition and responding to the EWG et al. petition; to the extent the issues in the petition impact the registration review case, EPA will incorporate its responses to the petition into its final registration review decision for glyphosate. To view the EWG et al. petition and related documents, visit docket ID: EPA-HQ-OPP-2019-0066 at regulations.gov.

The glyphosate registration review case covers glyphosate acid (PC code 417300) and the following salt forms with active pesticide registrations: isopropylamine salt (PC code 103601), ammonium salt (PC code 103604), ethanol amine salt (PC code 103605), diammonium salt (PC code 103607), dimethyl ammonium salt (PC code 103608), and the potassium salt (PC code 103613). Glyphosate is a non-selective, systemic herbicide with products registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, cereal grains, and other field crops. Non-agricultural uses include residential spot treatments, aquatic areas, forests, rights-of-way, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land. Glyphosate products are also registered for use on the glyphosate-resistant crops, including alfalfa, corn, soybean, cotton, canola, and sugar beets. The first pesticide product containing glyphosate was registered in 1974; a Reregistration Eligibility Decision (RED) for glyphosate was completed in 1993. Since then, the EPA has reviewed the risk assessments for glyphosate to determine if updates were necessary when new uses were added to glyphosate labels.

This document describes any changes since the Proposed Interim Registration Review Decision (PID), includes a summary of public comments on the PID, and includes the agency's interim registration review decision and the agency's rationale. See the PID for a summary of glyphosate's registration review timeline, use and usage information describing how and why glyphosate is used, the EPA's risk and benefits assessments, and a discussion of risk characterization. The PID also describes the mitigation measures that were proposed to address risks of concern and the regulatory rationale for the EPA's proposed interim registration review decision.

A. Updates Since the Proposed Interim Registration Review Decision was Issued

In April 2019, the EPA published the PID for glyphosate. Since that time, the agency has reviewed public comments and has made changes to the spray drift management labeling and rotational crop timing language that was proposed in the PID. The changes for spray drift management labeling are as follows: changes in droplet size restrictions, the removal of advisory spray drift statements for airblast applications, and the incorporation of updated swath displacement language for aerial applications. In addition, the agency has updated the language regarding rotational crop timing to provide clearer directions for use. For more information on the changes made to the mitigation proposed in the PID, please refer to Section IV.A. and Appendix A. There have been no additional updates to what was proposed in the PID, nor any updates to the draft risk assessments (DRAs). This document thus finalizes the agency's draft supporting documents *Glyphosate Draft Human Health Risk Assessment for Registration Review* and *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*,

which are available in the public docket. Along with the ID, the following documents are also posted to the glyphosate docket:

- *Response from the Pesticide Re-evaluation Division to Comments on the Glyphosate Proposed Interim Decision*, dated January 16, 2019
- *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment*, dated January 13, 2019

B. Summary of Public Comments on the Proposed Interim Decision and Agency Responses

During the 60-day public comment period for the PID, which opened on May 6, 2019, the agency received comments requesting an extension of the public comment period from the original deadline of July 5, 2019. The agency extended the comment period for 60 days, which then closed on September 3, 2019. During the 120-day comment period, the agency received roughly 283,300 comments. Over 12,000 unique submissions were received from various stakeholders, including glyphosate registrants, grower groups, non-governmental organizations, pesticide industry groups, states, the U.S. Department of Agriculture and members of the general public. Most comments came from mass mailer campaigns, and approximately 120 unique substantive comments were received from various stakeholders.

Along with the ID, the agency is posting the following documents that address comments received on the PID: *Response from the Pesticide Re-evaluation Division to Comments on the Glyphosate Proposed Interim Decision* and *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment*. Most of the comments received on the PID are substantively the same as comments received during previous glyphosate comment periods on the agency's risk assessments. The *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment* responds to comments that have not been addressed previously via the December 2016 FIFRA Scientific Advisory Panel (SAP) meeting to discuss the carcinogenic potential of glyphosate¹ or in previous registration review documents for glyphosate. These comments did not result in changes to the agency's risk assessments.

EPA's *Response from the Pesticide Re-evaluation Division to Comments on the Glyphosate Proposed Interim Decision* document combined comments by topic instead of responding to individual stakeholders and directs the public to responses previously provided in EPA documents. Comments specific to the glyphosate mitigation, comments of a broader regulatory nature, and the agency's responses to those comments are summarized below, and some resulted in changes to the mitigation proposed in the PID.

For more detailed responses to comments relating to the human health risk assessment, and EPA's cancer evaluation for glyphosate, see the *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* and *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment*. For more detailed responses to

¹ Materials from the December 13-16, 2016 FIFRA SAP are posted in docket EPA-HQ-OPP-2016-0385. The final report, the transcript, charge questions, and other materials are also available online: <https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel>

comments relating to the ecological risk assessment, see the *Response to Public Comments on the Preliminary Ecological Risk Assessment for Glyphosate*. For detailed responses to comments on the use/usage of glyphosate and the benefits, see the *Glyphosate: Response to Comments, Usage, and Benefits* (PC Codes: 103601, 103604, 103605, 103607, 103613, 417300). All response to comments documents are available in the public docket for glyphosate (EPA-HQ-OPP-2009-0361) and published online². The agency thanks all commenters for their comments and has considered them in developing this ID.

Comments Regarding the Environmental Working Group (EWG) Petition

Comment: On September 27, 2018, the agency received a petition from the Environmental Working Group, Ben & Jerry's Homemade, Inc., Happy Family Organics, MegaFood, MOM's Organic Market, National Co-op Grocers, Nature's Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farms, Inc (EWG et al.). The petitioners requested that the agency reduce the tolerance of the pesticide glyphosate in or on oats from 30 ppm to 0.1 ppm and modify labels to explicitly prohibit preharvest use on oats. The petitioners asserted that the current tolerance level for oats is not protective enough when assessing people's dietary exposure to glyphosate in oats and the potential carcinogenicity of glyphosate. Numerous members of the general public commented in support of the EWG et al. petition. Various stakeholders and numerous farmers commented in opposition of the petition. EWG et al. also provided comments on the PID that were similar in nature to the issues raised in the petition.

EPA Response: In accordance with FFDCA section 408(d)(3), EPA published EWG et al.'s petition for a 30-day public comment period on May 6, 2019; the public comment period closed on June 5, 2019. The full petition is posted in docket EPA-HQ-OPP-2019-0066 at www.regulations.gov. The agency is still reviewing the 103,447 comments that were received on the petition. This Interim Decision reflects the conclusions of EPA's most recent risk assessments and does not address the claims raised in the petition, or constitute EPA's response to the petition. The agency anticipates issuing the response to the petition in 2020.

Comments Regarding the Human Health Risk Assessment

Comment: The agency received comments regarding the human health risk assessment from a wide array of stakeholders. Topics included concerns with the cancer assessment, toxicological studies, protection of children, and detections of glyphosate. Additionally, open literature studies were also identified for the agency's consideration.

EPA Response: Comments received regarding the human health risk assessment for glyphosate have been previously addressed in the *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* (EPA-HQ-OPP-2009-0361-2343). Many of the open literature studies were previously identified and considered by the agency as part of two open literature searches. The remaining studies identified during the public comment period were primarily journal articles published since these searches were conducted. None of the open literature

² <https://www.epa.gov/ingredients-used-pesticide-products/proposed-interim-registration-review-decision-and-responses-0>

studies identified for the agency's consideration were found to have an impact on the glyphosate hazard characterization, cancer assessment, or human health risk assessment. The agency will continue to monitor the open literature for studies that use scientifically sound and appropriate methodology and relevant routes of exposure that have the potential to impact the risk evaluation of glyphosate. For more information, please see the *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment*, which is available on the public docket.

Comments Regarding Spray Drift Management

Comment: Several stakeholders, including USDA and NAAA, provided comments on the proposed droplet size requirement of "fine or coarser," suggesting that a larger droplet size may be more appropriate for glyphosate products where glyphosate is the only active ingredient. The commenters expressed concern that using a fine droplet size might increase the risk of drift while providing no improvement on efficacy, due to the fact that glyphosate is a systemic herbicide that needs less coverage than contact pesticides. Commenters also noted that glyphosate is often tank-mixed with other pesticides and that fine droplet size may be appropriate in those cases to allow greater flexibility for tank mixing.

EPA Response: The agency is requiring label changes to reduce off-target spray drift and establish a baseline level of protection against spray drift that is consistent across all products containing glyphosate. The agency's goal is to manage off-target spray drift from application of glyphosate while continuing to preserve glyphosate's utility for growers and allow growers continued flexibility when making applications. Since glyphosate is a systemic herbicide, the agency agrees that "medium" or coarser droplet size is appropriate when glyphosate is sprayed as the sole active ingredient, or when tank-mixed with other systemic herbicides. Since glyphosate is a compound that is frequently tank-mixed with other pesticides (e.g. when used with an insecticide in a burndown treatment), the agency agrees that a "fine" droplet size is appropriate when tank-mixing with a pesticide product that requires a fine droplet size. The agency is revising the droplet size labeling based on the comments received. Refer to Section IV.A.1. and Appendix B of this Interim Decision for additional information on the required droplet size language.

Comment: Commenters noted that it is not appropriate to require enforceable spray drift management language for airblast applications, given that herbicides are not applied via airblast to orchards and vineyards.

EPA Response: The agency agrees that airblast application is not an approved application method for glyphosate and has removed this language from the required labeling in Appendix B.

Comments Regarding Rotational Crop Timing

Comment: The Joint Glyphosate Task Force (JGTF), consisting of 26 member companies, commented on the proposed labeling changes for rotational crop timing, suggesting language that provides clearer directions for use.

EPA Response: The agency thanks the JGTF for their comment. The agency has reviewed the suggested language and agrees that the language is more informative and clarifies the directions for use regarding rotational crop timing. Updated label clarification language for rotational crop timing has been included in Appendix B.

Comments Regarding the JGTF “Glyphosate Master Reference Label”

Comment: The JGTF submitted to the agency a document titled “Glyphosate Master Reference Label,” which is intended to be used by registrants to aid in the creation and review of product labels containing glyphosate. The “Glyphosate Master Reference Label” intends to define key elements of a glyphosate end-use product label, including precautionary and other label statements, approved crop and non-crop uses, maximum application rates, methods of application, and application restrictions for specific uses.

EPA Response: The agency appreciates the registrant collaboration in identifying currently registered uses of glyphosate in the JGTF’s “Glyphosate Master Reference Label”. The task force developed this tool as a reference for registrants. While the JGTF’s “Glyphosate Master Reference Label” may be used by registrants to aid in label submission, EPA emphasizes that the existing EPA process for reviewing labels as part of registration review still applies.

II. USE AND USAGE

Glyphosate is a broad-spectrum, systemic glycine herbicide which inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase in plants and inhibits aromatic amino acid synthesis. It is the only herbicide in the Weed Science Society of America’s (WSSA) group 9 class and it has a unique mode of action. Glyphosate products are registered as ready-to-use solution, water-dispersible granules, soluble concentrate, emulsifiable concentrate, flowable concentrate, water soluble packaging, pressurized liquid, pellets/tablets, and tree injection shells. It can be applied as a pre-emergent, post-emergent, or as a pre-harvest application to the crop to treat a variety of emerged grass and broadleaf weeds. In a few crops (*e.g.* sugarcane), glyphosate is used as a plant growth regulator.

Glyphosate products are registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, legumes, cereal grains, and other field crops. Glyphosate products are also registered for use on the following glyphosate-resistant (transgenic) crops: corn, soybean, cotton, canola, sugar beets, and alfalfa. Registered non-agricultural uses include: tree injections, residential spot treatments, aquatic areas, forests, rights-of-way, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land.

Application methods vary for glyphosate and include aircraft, various ground equipment, and various handheld equipment. Application types include: aerial spray, ground boom spray, strip treatment, band treatment, broadcast spray, spot treatment, stump treatment, tree injection, and wipe-on/wiper treatments. The maximum single application rate on labels is up to 8 pounds acid equivalent per acre (lb ae/A) (acid equivalents or ae are used to assess the different acid and salt forms of glyphosate) for the following uses: pastures, non-food tree crops, forestry, aquatic

areas, and non-crop. However, for agricultural row crop uses, maximum single application rates are 1.55 lb ae/A for aerial applications and 3.75 lb ae/A for ground applications. Maximum annual application rates are generally 6 to 8 lbs ae/A, except for residential spot treatments.

The EPA completed a usage analysis for glyphosate by analyzing agricultural market research data from 2012 to 2016. Approximately 281 million pounds of glyphosate was applied to 298 million acres annually in agricultural settings, on average. Most glyphosate was applied to soybean (117.4 million lbs applied annually), corn (94.9 million lbs applied annually), and cotton (20 million lbs applied annually). Many citrus fruits (*e.g.*, grapefruit, oranges, lemons), field crops (*e.g.*, soybean, corn, cotton), and tree nuts (*e.g.*, almonds, walnuts, pistachios) have the highest percentage of their acres treated with glyphosate.

Approximately 24 million pounds of glyphosate are applied to non-agricultural sites annually, on average. The majority of non-agricultural use is in the homeowner market (5 million lbs applied annually), turf (4.9 million lbs applied annually), forestry (3.6 million lbs applied annually), and roadways (3.3 million lbs applied annually).

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

A summary of the agency's human health risk assessment was presented in the glyphosate PID. The agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of glyphosate. The EPA thoroughly assessed risks to humans from exposure to glyphosate from all registered uses and all routes of exposure and did not identify any risks of concern.

Both non-cancer and cancer effects were evaluated for glyphosate and its metabolites, aminomethyl phosphonic acid (AMPA) and N-acetyl-glyphosate. The human health risk assessment for glyphosate and supporting documents, including the agency's revised issue paper on the carcinogenic potential of glyphosate, are published in the public registration review docket for glyphosate (EPA-HQ-OPP-2009-0361) at www.regulations.gov. The deliberations of the glyphosate FIFRA SAP meeting on the carcinogenic potential of glyphosate, including the agenda, meeting notes, SAP recommendations, the EPA's presentation to the FIFRA SAP, and other supporting documents are published in the glyphosate FIFRA SAP docket (EPA-HQ-OPP-2016-0385) at www.regulations.gov.

The agency concluded that there are no dietary risks of concern for any segment of the population, even with the most conservative assumptions applied in its assessments (*e.g.*, tolerance-level residues, direct application to water, and 100% crop treated). The agency also concluded that there are no residential, non-occupational bystander, aggregate, or occupational risks of concern.

The EPA has not made a common mechanism of toxicity to humans finding as to glyphosate and any other substance and it does not appear to produce a toxic metabolite produced by other substances. Therefore, it was not appropriate for EPA to assess cumulative risks.

For additional details on the human health assessment for glyphosate, see the *Glyphosate Draft Human Health Risk Assessment for Registration Review*, which is available in the public docket.

1. Human Incidents and Epidemiological Analysis

The EPA conducted human health incident reviews for glyphosate in February 2014 and in October 2018. Thousands of glyphosate incidents were reported but most reported incidents were minor in severity. The high number of reported incidents across the databases is likely a result of glyphosate being among the most widely-used pesticides in the United States by volume. Health effects reported in the incident databases included dermal, ocular, and respiratory symptoms and effects were generally mild and resolved rapidly. While the agency recently received information regarding litigation related to glyphosate human health incident claims, submitted under the FIFRA 6(a)2 adverse event reporting requirement, the agency does not comment on private litigation. EPA has thoroughly evaluated potential human health risk associated with exposure to glyphosate and determined that there are no risks to human health from the current registered uses of glyphosate and that glyphosate is not likely to be carcinogenic to humans. The agency will continue to monitor incident information and additional analyses will be conducted if ongoing human incident monitoring indicates a concern.

The medical-case literature was reviewed, and most accidental ingestion of glyphosate formulations result in mild symptoms. Intentional ingestions caused moderate to severe symptoms and involved multiple organ systems.

The epidemiological literature was also reviewed but most studies were hypothesis-generating in nature. The EPA found there was insufficient evidence to conclude that glyphosate plays a role in any human diseases. Since the last EPA review of the epidemiological literature, two studies regarding the association between glyphosate exposure and non-Hodgkin's Lymphoma (NHL) were identified for detailed review by the agency; however, these studies did not impact the agency's assessment. For more information, refer to *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment*, which is available on the public docket.

For more information on reported human incidents, see the *Glyphosate: Tier II Incident Report*, available in the in the public docket for glyphosate.

2. Tolerances

Tolerances are established for residues of glyphosate in/on numerous plant commodities in 40 CFR § 180.364. Glyphosate tolerances range from 0.2 to 400 ppm. The EPA evaluated the glyphosate residue chemistry database to determine if the established tolerances conform to current practices and to determine whether updates were necessary for current crop group/subgroup definitions. The EPA intends to establish new tolerances for various vegetable and fruit groups and subgroups, as listed in Table 1. Upon establishment of these new crop group tolerances, EPA intends to remove the following individual tolerances, since they will no longer be needed: acerola; aloe vera; ambarella; asparagus; atemoya; avocado; bamboo, shoots; banana; biriba; breadfruit; cactus, fruit; cactus, pads; canistel; cherimoya; custard apple; date, dried fruit;

durian; feijoa; fig; fruit, stone, group 12; guava; ilama; imbe; imbu; jaboticaba; jackfruit; longan; lychee; mamey apple; mango; mangosteen; marmaladebox; noni; nut, tree, group 14; olive; palm heart; papaya; papaya, mountain; passionfruit; pawpaw; persimmon; pineapple; pistachio; pomegranate; pulasan; rambutan; rose apple; sapodilla; sapote, black; sapote, mamey; sapote, white; soursop; Spanish lime; star apple; starfruit; sugar apple; Surinam cherry; tamarind; vegetable, leafy, brassica, group 5; vegetable, leafy, except brassica, group 4; watercress, upland; and wax jambu. Additionally, EPA is requiring eliminating trailing zeros listed in tolerances consistent with agency policy.

Table 1. Required Changes to the Tolerance Levels or Commodity Definitions for Glyphosate.				
Current		Required Change		Comment
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)	
Soybean, forage	100.0	Soybean, forage	100	Correct number of significant figures to be consistent with EPA policy
Soybean, hay	200.0	Soybean, hay	200	
Soybean, hulls	120.0	Soybean, hulls	120	
Soybean, seed	20.0	Soybean, seed	20	
Fruit, stone, group 12	0.2	Fruit, stone, group 12-12	0.2	Update to the current crop group definitions; coconut was excluded from the tree nut crop group tolerances as the residues were not within 5x (coconut tolerance at 0.1 ppm)
Nut, tree, group 14	1.0	Nut, tree, group 14-12 (except coconut)	1.0	
Vegetable, leafy, except brassica, group 4	0.2	Vegetable, leafy, group 4-16	0.2	Update to the current crop group definitions
Vegetable, leafy, brassica, group 5	0.2	Vegetable, <i>Brassica</i> , head and stem, group 5-16	0.2	
Several	0.2-0.5--	Vegetable, stalk and stem, subgroup 22A	0.5	
	0.2	Vegetable, leaf petiole, subgroup 22B	0.2	
	0.2	Fruit, tropical and subtropical, edible peel, group 23	0.2	
	0.2	Fruit, tropical and subtropical, small fruit, inedible peel, group 24A	0.2	
	0.2	Fruit, tropical and subtropical, medium to large fruit, smooth, inedible peel, group 24B	0.2	
	0.2	Fruit, tropical and subtropical, large fruit, rough or hairy, inedible peel, group 24C	0.2	
	0.2	Fruit, tropical and subtropical, vine, inedible peel, group 24E	0.2	

In accordance with FFDCA, the agency will be conducting rulemaking to implement any tolerance changes identified for glyphosate.

As noted in the PID, the agency received a September 27, 2018 petition from the Environmental Working Group et al., requesting that the agency reduce the tolerance of the pesticide glyphosate in or on oats and modify labels to explicitly prohibit preharvest use on oats. The agency issued a Federal Register Notice of Filing for public comment in a separate docket, EPA-HQ-OPP-2019-0066. This Interim Decision reflects the conclusions of EPA's most recent risk assessments and

does not address the claims raised in the petition or provide EPA's response to the petition. The agency anticipates issuing the response to the petition in 2020.

3. Human Health Data Needs

No additional human health data needs have been identified for the glyphosate registration review beyond the human health data required as part of the registration review DCI, which has been satisfied.

B. Ecological Risks

A summary of the agency's ecological risk assessment was presented in the PID. The agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of glyphosate.

The agency did not identify potential risks of concern for fish, aquatic invertebrates, or aquatic-phase amphibians. Low or limited potential risks of concern were identified for mammals and birds. Consistent with its mode of action as an herbicide, potential risks to non-target terrestrial and aquatic plants were primarily from spray drift and the resulting distances from the edge of the field to below toxicity threshold were heavily dependent on the application rate used. Given its importance as a critical food resource for the monarch butterfly, the agency also completed a spray drift analysis for common milkweed, with those results being similar to distances calculated for other terrestrial plants tested in ecotoxicity tests (*i.e.*, cucumber).

Based on an adult honey bee acute contact and oral toxicity tests, the likelihood of acute adverse effects to adult bees is considered low at application rates up to 5.7 lb a.e./A; however, it is uncertain if effects would occur at higher application rates (*i.e.*, up to 8 lb a.e./A). In a colony-level study, no adverse effects (acute or sublethal) were reported based on exposure to residues from an application at a rate of 1.92 lb ae/A. However, the full suite of Tier I toxicity studies are unavailable to fully assess potential risk to bees at the individual and/or colony level.

The agency believes that additional data may be necessary to fully evaluate risks to bees. Although the agency did not identify the need for these additional data to evaluate potential effects to bees when initially scoping the registration review for glyphosate, the Problem Formulation and registration review generic data call-in (GDCI) for glyphosate were both issued prior to publication of the June 2014 harmonized *Guidance for Assessing Pesticide Risks to Bees*³. This 2014 guidance lists additional laboratory-based studies of individual bees and based on the results of those studies, possible colony-level studies, that were not included in the glyphosate registration review GDCI. Therefore, the agency is currently determining whether additional bee toxicity and exposure data are needed for glyphosate. If the agency determines that additional data are necessary to help make a final registration review decision for glyphosate, then EPA will issue a GDCI to obtain these data. The pollinator studies that could be required for glyphosate are listed in Table 2.

³http://www2.epa.gov/sites/production/files/201406/documents/pollinator_risk_assessment_guidance_06_19_14.pdf

Table 2: Potential Pollinator Data Requirements

Guideline #	Study
Tier 1	
850.3020	Acute contact toxicity study with adult honey bees
850.3030	Honey bee toxicity of residues on foliage
Non-Guideline (OECD 213)	Honey bee adult acute oral toxicity
Non-Guideline (OECD 237)	Honey bee larvae acute oral toxicity
Non-Guideline (OECD 245)	Honey bee adult chronic oral toxicity
Non-Guideline OECD 239)	Honey bee larvae chronic oral toxicity
Tier 2 [†]	
Non-Guideline	Field trial of residues in pollen and nectar
Non-Guideline (OECD 75)	Semi-field testing for pollinators
Tier 3 [†]	
850.3040	Full-Field testing for pollinators

[†] The need for higher tier tests for pollinators will be determined based upon the results of lower tiered tests and/or other lines of evidence and the need for a refined pollinator risk assessment.

The EPA is currently working with its federal partners and other stakeholders to implement an interim approach for assessing potential risk to listed species and their designated critical habitats. Once the scientific methods necessary to complete risk assessments for listed species and their designated critical habitats are finalized, the agency will complete its endangered species assessment for glyphosate. The draft biological evaluation for glyphosate is anticipated in 2020.

The agency conducted a review of ecological incidents and determined the majority of the glyphosate incidents are for terrestrial plants. Most plant incidents involved spray drift onto adjacent agricultural crops and grass. Fewer incidents were reported for terrestrial and aquatic wildlife.

For additional details on the ecological assessment for glyphosate, see the *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*, which is available in the public docket.

1. Ecological and Environmental Fate Data Needs

The ecological effects data required as part of the glyphosate registration review DCI were received and found to be adequate for risk assessment. The agency will issue a DCI for additional pollinator data as part of a separate action if it determines that additional pollinator data are necessary to help make a final registration review decision for glyphosate.

C. Benefits Assessment

Glyphosate is the most commonly used agricultural herbicide in the United States. It is a broad-spectrum herbicide that provides postemergence control of broadleaf, sedge, and grass weeds with minimal residual toxicity to crops or non-target vegetation. Glyphosate is a unique herbicide as it is the only herbicide classified as a Group 9 herbicide by the WSSA, which acts by inhibiting the enzyme EPSP synthase in plants and inhibiting aromatic amino acid synthesis.

Glyphosate is a relatively inexpensive herbicide to apply in agricultural situations, with the cost of applications to most crops ranging \$1 to \$13 per acre.

Glyphosate products are registered for use in agriculture, including horticulture, viticulture, and silviculture, as well as non-agricultural sites including commercial, industrial, and residential areas. Current glyphosate-resistant field crops are soybean, corn, cotton, canola, alfalfa, and sugar beet. Many of these crops, such as corn, cotton, soybean, and sugar beet, have exceptionally high percentages of their acreage treated with glyphosate (approximately 90 percent of acres treated in each crop). Genetically-engineered (transgenic) glyphosate-resistant (GR) varieties of these crops can be sprayed over-the-top with minimal or no crop phytotoxicity, and glyphosate may also be used as a pre-plant burndown in many of these crops. On average, 84 percent of glyphosate applied in agricultural settings, in terms of pounds, is applied to soybeans, corn, or cotton per year.

Glyphosate is also beneficial as part of weed control programs in orchards and specialty crops. Glyphosate use is prevalent in orchards and vineyards, and most acres of crops such as tree nuts, citrus, and grapes are treated with glyphosate. Glyphosate is the most versatile herbicide in orchard floor management because it may be used for under tree weed control, chemical wiping, chemical mowing, and spot treatment. Since glyphosate controls a broad spectrum of weeds and does not have residual soil activity, it can be used to control emerged weeds prior to planting high value crops such as fruits and vegetables, for which growers sometimes have limited weed control options.

Glyphosate is also important for noxious and invasive weed control in aquatic systems, pastures/rangelands, public lands, forestry, and rights-of-way. Invasive weeds controlled by glyphosate include cattails and water hyacinth, which can impede water flow and irrigation. Improper weed management can cause water to stagnate, providing a breeding habitat for mosquitos. Therefore, effective weed control is important for controlling mosquito-borne diseases. Glyphosate is also important for habitat restoration efforts. It is used to control invasive annual, perennial, and woody plants in riparian habitats and rangeland. Glyphosate use in rights-of-way helps keep roadways and railroad tracks safe by protecting the stability of the surface, maintaining visibility for operators, and allowing for the distribution of goods, services, and utilities (gas and electric). Glyphosate is the most frequently used active ingredient used to control invasive species in the United States.

Glyphosate is a versatile active ingredient and can be applied with many different types of application equipment depending on the needs of the user. In addition to the broadcast spray applications, it can be applied via application methods such as cut stump treatment, stem/tree injection, wick applications, spot treatment, and as a directed spray.

For more information on the benefits of glyphosate, see the *Glyphosate: Response to Comments, Usage, and Benefits*. In addition, the USDA provided non-agricultural usage information as a 2018 comment in the glyphosate public docket (EPA-HQ-OPP-2009-0361-1618), which furthered the agency's understanding of the benefits of glyphosate to this sector.

IV. INTERIM REGISTRATION REVIEW DECISION

A. Risk Mitigation and Regulatory Rationale

The EPA did not identify any human health risks from exposure to glyphosate. The agency identified potential ecological risk to mammals and birds, but these risks are expected to be limited to the application area or areas near the application area. The EPA also identified potential risk to terrestrial and aquatic plants from off-site spray drift, consistent with glyphosate's use as an herbicide.

Glyphosate is a versatile herbicide that provides a broad spectrum of weed control across numerous agricultural and non-agricultural sites. Glyphosate is generally inexpensive in agricultural settings. Glyphosate is important in the management of invasive/noxious weeds and is a critical tool for habitat restoration efforts for rangeland and pastures. It is used for weed management for rights-of-way, forestry, industrial settings, residential areas, and aquatic environments.

The EPA concludes that the benefits outweigh the potential ecological risks when glyphosate is used according to label directions. To reduce off-site spray drift to non-target organisms, the agency is requiring spray drift management labeling. Since the PID was issued and in response to comments, the agency has made changes to the spray drift management language relating to droplet size, updated the swath displacement language based on current EPA policy, and removed the proposed advisory spray drift language for application via airblast, as airblast is not an application method used for glyphosate. In addition, EPA has adjusted the required language for rotational crop timing information based on the comments received. All required mitigation measures are detailed in Appendices A and B.

1. Spray Drift Management

The agency is requiring label changes to reduce off-target spray drift and establish a baseline level of protection against spray drift that is consistent across all glyphosate products. Reducing spray drift will reduce the extent of environmental exposure and risk to non-target plants and animals. Although the agency is not making a complete endangered species finding at this time, these label changes are expected to reduce the extent of exposure and may reduce risk to listed species whose range and/or critical habitat co-occur with the use of glyphosate.

The agency is requiring the following spray drift mitigation language to be included on all glyphosate product labels for products applied by liquid spray application. The required spray drift language is intended to be mandatory, enforceable statements and supersede any existing language already on product labels (either advisory or mandatory) covering the same topics. The agency is providing recommendations which allow glyphosate registrants to standardize all advisory language on glyphosate product labels. Registrants must ensure that any existing advisory language left on labels does not contradict or modify the new mandatory spray drift statements required in this ID once added to the labels.

- Applicators must not spray during temperature inversions.

- For aerial applications, do not apply when wind speeds exceed 15 mph at the application site. If the wind speed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor blade diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.
- For aerial applicators, if the windspeed is 10 miles per hour or less, applicators must use $\frac{1}{2}$ swath displacement upwind at the downwind edge of the field. When the windspeed is between 11-15 miles per hour, applicators must use $\frac{3}{4}$ swath displacement upwind at the downwind edge of the field.
- For aerial applications, the release height must be no higher than 10 feet from the top of the ground or crop canopy, unless a greater application height is required for pilot safety.
- For ground boom applications, apply with the release height no more than 4 feet above the ground or crop canopy.
- For ground and/or aerial applications, select nozzle and pressure that deliver Medium or coarser droplets as indicated in nozzle manufacturer's catalogues and in accordance with American Society of Agricultural & Biological Engineers Standard 572.1 (ASABE S572.1), unless tank-mixing with a pesticide product that requires use of a finer droplet size (ASABE S572.1). If a finer droplet size is used, applicators are required to use a Fine or coarser droplet size (ASABE S572.1).

The agency's goal is to manage off-target spray drift from applications of glyphosate while continuing to preserve glyphosate's utility for growers and allow growers continued flexibility when making applications. The agency assessed the potential impact on growers of the required spray drift management restrictions and has determined that these measures are not expected to substantially reduce the benefits of glyphosate to users. Prohibiting glyphosate applications during temperature inversions may impact the usability of glyphosate products by reducing the amount of time users have to apply glyphosate, but growers can switch to other products if they encounter temperature inversions.

For the PID, the EPA considered the impact of requiring "fine" or coarser droplets (*i.e.*, requiring growers to deliver droplets no smaller than "fine") on glyphosate labels and determined that such a requirement was not likely to affect the efficacy of glyphosate when used alone since it is a systemic herbicide. The agency is now requiring "medium" or coarser droplet size where glyphosate is the sole active ingredient being applied in order to further reduce drift. Efficacy is anticipated to be unaffected based on comments received from the public. Glyphosate is a compound that is frequently tank-mixed with other herbicides. Given that the language provides flexibility with droplet size for tank-mixed partners, the EPA does not expect there would be concerns for tank mixing with other herbicides. However, since glyphosate can be applied as a burndown treatment, insecticides may be included in the tank mix. Insecticides are generally considered to provide better efficacy with smaller droplets, therefore EPA is allowing "fine" droplets for use in tank mixes with active ingredients that require "fine" or coarser droplets. The EPA is uncertain if requiring "fine" droplets will impact the efficacy of insecticides tank-mixed with glyphosate because some insecticides could be more effective at droplet sizes smaller than "fine" (such as "very fine" or "extremely fine"). If reduced efficacy occurred, the agency would expect growers to respond by increasing the application rates (if allowed by the label), increasing

the number of applications, increasing the application rates of tank-mix partners, making additional applications, or switching to a different active ingredient.

In addition to including the spray drift restrictions on glyphosate labels, all references to volumetric mean diameter (VMD) information for spray droplets are required to be removed from all glyphosate labels where such information currently appears. The new language above, which cites ASABE S572.1, eliminates the need for VMD information.

2. Herbicide Resistance Management

On August 24, 2017, the EPA finalized a Pesticide Registration Notice (PRN or Notice) on herbicide resistance management.⁴ Consistent with the Notice, the EPA is requiring the implementation of herbicide resistance measures for existing chemicals during registration review, and for new chemicals and new uses at the time of registration. In registration review, herbicide resistance elements will be included in every herbicide PID and ID.

The development and spread of herbicide-resistant weeds in agriculture is a widespread problem that has the potential to fundamentally change production practices in U.S. agriculture. While herbicide-resistant weeds have been known since the 1950s, the number of species and their geographical extent has been increasing rapidly. Currently there are over 250 weed species worldwide with confirmed herbicide resistance. In the United States, there are over 155 weed species with confirmed resistance to one or more herbicides.

Management of herbicide-resistant weeds, both in controlling established herbicide-resistant weeds and in slowing or preventing the development of new herbicide-resistant weeds, is a complex problem without a simple solution. Coordinated efforts of growers, agricultural extension, academic researcher, scientific societies, pesticide registrants, and state and federal agencies are required to address this problem.

The EPA is requiring measures for the pesticide registrants to provide growers and users with detailed information and recommendations to slow the development and spread of herbicide resistant weeds. This is part of a more holistic, proactive approach recommended by crop consultants, commodity organizations, professional/scientific societies, researchers, and the registrants themselves.

3. Non-target Organism Advisory

The protection of pollinators and other non-target organisms is a priority for the agency. While the agency did not identify risks to individual bees from glyphosate applications at rates below 5.7 lb ae/A, risks to terrestrial invertebrates at higher application rates are uncertain. In addition, glyphosate may impact non-target plants via spray drift and impact nectar sources and habitat for pollinators and other non-target organisms. EPA is requiring a non-target organism advisory to alert users of potential impact to non-target organisms: “This product is toxic to plants and may adversely impact the forage and habitat of non-target organisms, including pollinators, in areas

⁴ PRN 2017-2, “Guidance for Herbicide Resistance Management Labeling, Education, Training, and Stewardship”

adjacent to the treated site. Protect the forage and habitat of non-target organisms by following label directions intended to minimize spray drift.”

4. Label Consistency Measures

There are currently 557 Section 3 registrations and 37 Section 24(c) registrations for glyphosate. Label directions for glyphosate vary significantly from label to label, and newer stamped labels in general have more comprehensive instructions than older labels. The EPA is requiring all glyphosate labels to be updated to modern standards. The specific components of the label that require updates are as follows: the maximum application parameters, the environmental hazards statement for aquatic use, and clarification on rotational crop timing. In addition, the agency is providing guidance to glyphosate registrants on acceptable marketing statements.

Maximum Application Parameters

In 2013, at the agency’s request and in preparation for risk assessment, the Joint Glyphosate Task Force, a consortium of glyphosate registrants, created a *Use Summary Matrix*, which was intended to summarize all use sites being supported as part of registration review and outline important application parameters such as maximum single and yearly application rates. EPA’s risk assessments for glyphosate were based on maximum application parameters as described in the *Use Summary Matrix*. The maximum application rates on glyphosate labels must be consistent with the maximum application rates that were assessed by the agency and supported by the Joint Glyphosate Task Force. These maximum application parameters are described in Appendix C of this document.

Many older glyphosate labels do not define any maximum application parameters. EPA is requiring that maximum application parameters be clearly defined on all glyphosate labels and must not exceed the maximum application parameters as described in Appendix C. It is not EPA’s intention to change the current application rates on glyphosate labels, but the agency is requiring defined rate limits in order to establish better consistency and clarity on labels. Appendix C lists the maximum application parameters by use site for both aerial and ground application.

Statements for Aquatic Uses

The EPA is requiring updated environmental hazards statements for aquatic use products to be consistent with modern standards and to be in line with newer pesticide labels. The glyphosate Reregistration Eligibility Decision (RED) issued in 1993 specified that glyphosate labels formulated for aquatic use have language intended to warn users of potential fish suffocation from aquatic applications. The EPA is requiring updates to the existing language to be consistent with current labeling guidance (see the EPA’s Label Review Manual, and Table 4 below).

An additional statement under “directions for use” for aquatic use labels is required to instruct users to apply in strips to help avoid oxygen depletion when emerged weed infestations cover the total surface area of an impounded water body (see Table 4 below).

Table 4. Statements Required for Glyphosate for Aquatic Use

Product Type	Statement
Environmental hazards: for labels with terrestrial uses only	“Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Environmental hazards: for labels with aquatic uses only	“Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Environmental hazards: for labels with both aquatic and terrestrial uses	“Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. For terrestrial uses, do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark [<i>Optional text, if applicable:</i> except when applying this product by air over the forest canopy]. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”
Directions for use for aquatic uses	“When emerged weed infestations cover the total surface area of an impounded waterbody, apply this product to the emerged vegetation in strips to help avoid oxygen depletion in the water due to decaying vegetation. Oxygen depletion in the water can result in increased fish mortality.”

Clarification on Rotational Crop Timing

Many glyphosate labels lack instructions for crop rotation. The EPA is requiring the clarification that treated fields may be rotated to a labeled crop at any time. For fields being rotated to a non-labeled crop, any glyphosate application must be made a minimum of 30 days prior to planting. EPA is updating the language that was proposed in the PID to further clarify the instructions on rotational crop timing based on public comments received.

Label Claims

During meetings with the agency in 2018, the Joint Glyphosate Task Force proposed to clarify on existing labels a statement about how glyphosate works. The following statement is being required: “Glyphosate works by targeting an enzyme that is essential for plant growth.” The revision is consistent with the requirements of 40 CFR § 156.10(a)(5). Registrants may use alternate claims, as long as alternate claims meet labeling requirements. Registrants can refer to 40 CFR § 156.10(a)(5) for requirements regarding label claims prior to submitting updated labels for registration review.

B. Tolerance Actions

The EPA is requiring the following revisions for glyphosate tolerances: adjusting the number of significant figures, establishing new tolerances for various vegetable and fruit groups/subgroups, and deleting certain older tolerances which are no longer needed due to the new tolerance

groupings. Refer to Section III.A.3 of this document for the required tolerance changes. The agency will use its FFDCA rulemaking authority to make the needed changes to the tolerances. The agency intends to address the tolerance revisions requested by the EWG et al. petitioners in its response to their petition and has not addressed them in this document.

C. Interim Registration Review Decision

In accordance with 40 CFR § 155.56 and 155.58, the agency is issuing this Interim Registration Review Decision. Except for the EDSP, ESA, and resolution of the EWG et al. petition, the agency has made the following Interim Registration Review Decision: (1) no additional data are required at this time; and (2) changes to the affected registrations and their labeling are needed, as described in Section IV. A. and Appendices B and C. This document finalizes the agency's draft supporting documents: *Glyphosate Draft Human Health Risk Assessment for Registration Review*, and *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*.

In this interim registration review decision, the EPA is making no human health or environmental safety findings associated with the EDSP screening of glyphosate, nor is it making a complete endangered species finding. This interim registration review decision does not address the specific claims raised in the EWG et al. petition, nor does it constitute EPA's response to the petition. Although the agency is not making a complete endangered species finding at this time, the mitigation described in this document is expected to reduce the extent of environmental exposure and may reduce risk to listed species whose range and/or critical habitat co-occur with the use of glyphosate. The agency's final registration review decision for glyphosate will be dependent upon the result of the agency's ESA assessment and any needed section 7 consultation with the Services, an EDSP FFDCA section 408(p) determination, and after a resolution of the EWG et al. petition.

D. Data Requirements

No additional data are required for this registration review at this time. The EPA will consider requiring the glyphosate registrants to submit pollinator data as a separate action.

V. NEXT STEPS AND TIMELINE

A. Interim Registration Review Decision

A Federal Register Notice will announce the availability of this Interim Registration Review Decision for glyphosate. A final decision on the glyphosate registration review case will occur after: (1) an EDSP FFDCA §408(p) determination, (2) an endangered species determination under the ESA and any needed §7 consultation with the Services, and (3) a resolution of the EWG et al. petition. This document finalizes the agency's draft supporting documents: *Glyphosate Draft Human Health Risk Assessment for Registration Review*, and *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*.

B. Implementation of Mitigation Measures

Given the anticipated timeframe for the agency's response to the EWG et al. petition in 2020, labels should not be submitted at this time. Once the agency completes its response to the petition, it will issue letters to glyphosate registrants requesting label submission to incorporate the glyphosate required interim risk mitigation (see Appendices A, B, and C), which will be posted to the docket. Revised labels and requests for amendment of registrations will be required for submission to the agency for review within 60 days following the issuance of letters.

Appendix A: Summary of Required Actions for Glyphosate

Registration Review Case#: 0178 PC Codes: 103601, 103604, 103605, 103607, 103608, 103613, 417300 Chemical Type: herbicide Chemical Family: glycine derivative Mode of Action: targets the 5-enolpyruvyl-3-shikimate phosphate synthase enzyme						
Affected Population(s)	Source of Exposure	Route of Exposure	Duration of Exposure	Potential Risk(s) of Concern	Required Actions	Comment
Terrestrial and aquatic plants	Spray drift	Foliar absorption	Acute Chronic	Survival, biomass	Require enforceable spray drift management language; updated environmental hazards language	
Birds	Residues on food items (via deposition or spray drift)	Dietary	Acute Chronic	Growth	Require enforceable spray drift management language	Risks are likely limited to the field and areas near the application field.
Mammals	Residues on food items (via deposition or spray drift)	Dietary	Acute Chronic	Growth and reproduction	Require enforceable spray drift management language	Risks to are likely limited to the field and areas near the application field.
Terrestrial invertebrates	Residues on nectar sources (via deposition or spray drift)	Dietary	Acute Chronic	Effects on nectar sources of terrestrial invertebrates	Non-target organism environmental hazards language	Risks to bees are uncertain at application rates higher than 1.9 lb ae/A. The agency may require additional pollinator data to fully assess risk to terrestrial invertebrates.

Appendix B: Required Labeling Changes for Glyphosate Products

Description	Required Label Language for Glyphosate Products				Placement on Label
	End Use Products				
Mechanism of Action Group Number	Note to registrant: • Include the name of the ACTIVE INGREDIENT in the first column • Include the word “GROUP” in the second column • Include the MODE/MECHANISM OF ACTION CODE in the third column (for herbicides this is the Mechanism of Action, for fungicides this is the FRAC Code, and for insecticides this is the Primary Site of Action) • Include the type of pesticide (<i>i.e.</i>, HERBICIDE or FUNGICIDE or INSECTICIDE) in the fourth column.				Front Panel, upper right quadrant. All text should be black, bold face and all caps on a white background, except the mode of action code, which should be white, bold face and all caps on a black background; all text and columns should be surrounded by a black rectangle.
	Glyphosate	GROUP	9	HERBICIDE	
Non-target Organism Advisory	“NON-TARGET ORGANISM ADVISORY: This product is toxic to plants and may adversely impact the forage and habitat of non-target organisms, including pollinators, in areas adjacent to the treated site. Protect the forage and habitat of non-target organisms by following label directions intended to minimize spray drift.”				Environmental Hazards
Environmental Hazards Statement for Aquatic Use	<i>For labels without aquatic uses:</i> “Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.” <i>For labels with aquatic uses only:</i> “Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.” <i>For labels with both aquatic and terrestrial uses:</i> “Killing aquatic weeds can result in depletion or loss of oxygen in the water due to decomposition of dead plant material. This oxygen loss can cause fish suffocation. Consult with your				Environmental Hazards

Description	Required Label Language for Glyphosate Products	Placement on Label
	State agency with primary responsibility for regulating pesticides before applying to public waters to determine if a permit is required. For terrestrial uses, do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark [<i>Optional text, if applicable:</i> except when applying this product by air over the forest canopy]. Do not contaminate water when cleaning equipment or disposing of equipment wash waters and rinsate.”	
Aquatic Use Statement	“When emerged weed infestations cover the total surface area of an impounded waterbody, apply this product to the emerged vegetation in strips to help avoid oxygen depletion in the water due to decaying vegetation. Oxygen depletion in the water can result in increased fish mortality.”	Directions for Use
HERBICIDE RESISTANCE MANAGEMENT: Weed Resistance Management	Include resistance management label language for herbicides from PRN 2017-1 and PRN 2017-2 (https://www.epa.gov/pesticide-registration/pesticide-registration-notice-year)	Directions for Use, prior to directions for specific crops under the heading “WEED RESISTANCE-MANAGEMENT”
Additional Required Labelling Action (Applies to all products delivered via liquid spray applications)	Remove information about volumetric mean diameter from all labels where such information currently appears.	Directions for Use
Rotational crop information	“This product may be applied during fallow intervals preceding planting, prior to planting or transplanting, at-planting, or preemergence to annual and perennial crops listed on this label, except where specifically limited. For any crop <u>not</u> listed on this label, application must be made a minimum of 30 days prior to planting.”	Directions for Use
Label claims	“Glyphosate works by targeting an enzyme that is essential for plant growth.” [Alternate claims, if used, must meet labeling requirements. Refer to 40 CFR § 156.10(a)(5) for requirements regarding label claims.]	Product Information
Clarification of application rates	Ground and aerial applications rates on the labels must not exceed the maximum application parameters as noted in Appendix C of this document, which were maximum application parameters assessed by the EPA. Application rates may only be clarified for uses that are currently approved on labels.	Directions for Use

Description	Required Label Language for Glyphosate Products	Placement on Label
Spray Drift Management Application Restrictions for all products that are delivered via liquid spray applications and allow aerial application	“MANDATORY SPRAY DRIFT Aerial Applications: - Do not release spray at a height greater than 10 ft above the ground or vegetative canopy, unless a greater application height is necessary for pilot safety. - Applicators are required to use a Medium or coarser droplet size (ASABE S572.1) unless tank-mixing with a pesticide product that requires use of a finer droplet size. If a finer droplet size is used, applicators are required to use a Fine or coarser droplet size (ASABE S572.1). - If the windspeed is 10 miles per hour or less, applicators must use ½ swath displacement upwind at the downwind edge of the field. When the windspeed is 11-15 miles per hour, applicators must use ¾ swath displacement upwind at the downwind edge of the field. - Do not apply when wind speeds exceed 15 mph at the application site. If the windspeed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters. - Do not apply during temperature inversions.”	Directions for Use, in a box titled “Mandatory Spray Drift” under the heading “Aerial Applications”
Spray Drift Management Application Restrictions for products that are delivered via liquid spray applications and allow ground boom applications	“MANDATORY SPRAY DRIFT Ground Boom Applications: - User must only apply with the release height recommended by the manufacturer, but no more than 4 feet above the ground or crop canopy. - Applicators are required to use a Medium or coarser droplet size (ASABE S572.1) unless tank-mixing with a pesticide product that requires use of a finer droplet size. If a finer droplet size is used, applicators are required to use a Fine or coarser droplet size (ASABE S572.1). - Do not apply when wind speeds exceed 15 miles per hour at the application site. - Do not apply during temperature inversions.”	Directions for Use, in a box titled “Mandatory Spray Drift” under the heading “Ground Boom Applications”
Spray Drift Management Application Restrictions for products that are delivered via liquid spray applications and allow boomless ground sprayer applications	“MANDATORY SPRAY DRIFT Boomless Ground Applications: - Applicators are required to use a Medium or coarser droplet size (ASABE S572.1) unless tank-mixing with a pesticide product that requires use of a finer droplet size. If a finer droplet size is used, applicators are required to use a Fine or coarser droplet size (ASABE S572.1). - Do not apply when wind speeds exceed 15 miles per hour at the application site. - Do not apply during temperature inversions.”	Directions for Use, in a box titled “Mandatory Spray Drift” under the heading “Boomless Applications”

Description	Required Label Language for Glyphosate Products	Placement on Label
Advisory Spray Drift Management Language for all products delivered via liquid spray application	“SPRAY DRIFT ADVISORIES THE APPLICATOR IS RESPONSIBLE FOR AVOIDING OFF-SITE SPRAY DRIFT. BE AWARE OF NEARBY NON-TARGET SITES AND ENVIRONMENTAL CONDITIONS. IMPORTANCE OF DROPLET SIZE An effective way to reduce spray drift is to apply large droplets. Use the largest droplets that provide target pest control. While applying larger droplets will reduce spray drift, the potential for drift will be greater if applications are made improperly or under unfavorable environmental conditions. Controlling Droplet Size – Ground Boom <i>(note to registrants: remove if ground boom is prohibited on product labels)</i> • Volume - Increasing the spray volume so that larger droplets are produced will reduce spray drift. Use the highest practical spray volume for the application. If a greater spray volume is needed, consider using a nozzle with a higher flow rate. • Pressure - Use the lowest spray pressure recommended for the nozzle to produce the target spray volume and droplet size. • Spray Nozzle - Use a spray nozzle that is designed for the intended application. Consider using nozzles designed to reduce drift. Controlling Droplet Size – Aircraft <i>(note to registrants: remove if aerial application is prohibited on product labels)</i> • Adjust Nozzles - Follow nozzle manufacturers’ recommendations for setting up nozzles. Generally, to reduce fine droplets, nozzles should be oriented parallel with the airflow in flight. BOOM HEIGHT – Ground Boom <i>(note to registrants: remove if ground boom is prohibited on product labels)</i> For ground equipment, the boom should remain level with the crop and have minimal bounce. RELEASE HEIGHT - Aircraft <i>(note to registrants: remove if aerial application is prohibited on product labels)</i> Higher release heights increase the potential for spray drift. SHIELDED SPRAYERS Shielding the boom or individual nozzles can reduce spray drift. Consider using shielded sprayers. Verify that the shields are not interfering with the uniform deposition of the spray on the target area. TEMPERATURE AND HUMIDITY When making applications in hot and dry conditions, use larger droplets to reduce effects of evaporation. TEMPERATURE INVERSIONS	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”

Description	Required Label Language for Glyphosate Products	Placement on Label
	Drift potential is high during a temperature inversion. Temperature inversions restrict vertical air mixing, which can cause small droplets to remain suspended in a concentrated cloud. This cloud can move in unpredictable directions due to the light variable winds common during inversions. Temperature inversions are characterized by increasing temperatures with altitude and are common on nights with limited cloud cover and light to no wind. They can begin to form in late afternoon/early evening and often continue into the morning. Their presence can be indicated by ground fog. If fog is not present, inversions can also be identified by the movement of smoke from a ground source or an aircraft smoke generator. Smoke that layers and moves laterally in a concentrated cloud (under low wind conditions) indicates an inversion, while smoke that moves upward and rapidly dissipates indicates good vertical air mixing. WIND Drift potential generally increases with wind speed. AVOID APPLICATIONS DURING GUSTY WIND CONDITIONS. Applicators need to be familiar with local wind patterns and terrain that could affect spray drift.”	
Advisory Spray Drift Management Language for products that are delivered via liquid spray applications and allow boomless ground sprayer applications	“SPRAY DRIFT ADVISORIES <u>Boomless Ground Applications:</u> • Setting nozzles at the lowest effective height will help to reduce the potential for spray drift.”	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”
Advisory Spray Drift Management Language for all products that allow liquid applications with handheld technologies	“SPRAY DRIFT ADVISORIES <u>Handheld Technology Applications:</u> • Take precautions to minimize spray drift.”	Directions for Use, just below the Spray Drift box, under the heading “Spray Drift Advisories”

Appendix C: Maximum Application Rates for Glyphosate Ground and Aerial Application⁵

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Round-up Ready 2 Yield Soybeans	3.75	1.55	6
Root Tuber Vegetables: arracacha, arrowroot, carrot, chinese artichoke, Jerusalem artichoke, beet (garden), burdock, canna, cassava (bitter and sweet), celeriac, chayote (root), chervil (turnip-rooted), chicory, chufa, dasheen (taro), galangal, ginger, ginseng, horseradish, leren, kava (turn-rooted), parsley (turnip-rooted), parsnip, potato, radish, rutabaga, oriental radish, salsify, skirret, sweet potato, taniel, turmeric, turnip, wasabi, yacon, yam bean, true yam	3.75	1.55	6
Rangelands	0.38	0.38	2.25
Pome Fruits: including apple, crabapple, loquat, mayhaw, pear, oriental pear, quince	3.75	1.55	8
Pastures	8	8	8
Oilseed Crops: borage, buffalo gourd, calendula, canola, castor oil plant, chinese tallow tree, crambe, cuphea, echium, euphorbia, evening primrose, flax (seed), gold of pleasure, hare's ear mustard, jojoba, lesquerella, meadow foam, milkweed, mustard (seed), niger (seed), oil radish, poppy seed, rapeseed, rose hip, safflower, sesame, stokes aster, sunflower, sweet rocket, tallow wood, tea oil plant, veronia.	3.75	1.55	6
Non-Food Tree Crops: pine, poplar, eucalyptus, christmas trees, other non-food tree crops	8	8	8
Miscellaneous Tree Food Crops: cactus (fruit and pads), palm (heart, leaves, oil)	3.75	1.55	8
Miscellaneous Crops: aloe vera, bamboo shoots, globe artichoke, okra, peanut (ground nut), strawberry, sugar beet, asparagus, pineapple	3.75	1.55	6
Legume Vegetables: Succulent varieties of Bean (Lupinus: includes grain lupin, sweet lupin, white lupin, white sweet lupin); Bean (Phaseolus: includes field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean, wax bean); Bean (Vigna: includes adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, yardlong bean); Broad bean (fava); Chickpea (garbanzo); Guar; Jackbean; Lablab bean; Lentil; Pea (Pisum: includes dwarf pea, edible-podded pea, English pea, field pea, garden pea, green pea, snowpea, sugar snap pea); Pigeon pea; Soybean (immature seed); Sword bean. Dry varieties of Bean (Lupinus: includes grain lupin, sweet lupin, white lupin, white sweet lupin); Bean (Phaseolus: includes field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean,	3.75	1.55	6

⁵ It is not EPA's intention to change the current application rates on glyphosate labels, but the agency is requiring defined rate limits on labels in order to establish better consistency and clarity on labels.

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
tepary bean, wax bean); Bean (Vigna: includes adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, yardlong bean); Broad bean (fava); Chickpea (garbanzo); Guar; Jackbean; Lablab bean; Soybean (immature seed); Sword bean Dry varieties of Lentil; Pea (Pisum: includes dwarf pea, edible-podded pea, English pea, garden pea, green pea, snowpea, sugar snap pea); Pigeon pea			
Leafy Vegetables: Amaranth (Chinese spinach); Arugula (rocket); Beet greens; Cardoon; Celery; Chinese celery; Celtuce; Chaya; Chervil; Edible-leaved chrysanthemum; Garland chrysanthemum; Corn salad; Cress (garden and upland); Dandelion; Dock (sorrel); Dokudami; Endive (escarole); Florence fennel; Gow kee; Lettuce (head and leaf); Orach, Parsley; Purslane (garden and winter); Radicchio (red chicory); Rhubarb; Spinach; New Zealand spinach; Vine spinach; Swiss chard; Watercress (upland); Water spinach	3.75	1.55	6
Herbs and Spices: Allspice, Angelica, Star anise, Annatto (seed), Balm, Basil, Corage, Burnet, camomile, Caper buds, Caraway, Black caraway, Cardamom, Cassia bark, Cassia buds, Catnip, Celery seed, Chervil (dried), Chive, Chinese chive, Cilantro (leaf), Cilantro (seed), Cinnamon, Clary, Clove buds, Coriander leaf (cilantro or Chinese parsley), Coriander seed (cilantro), Costmary, Cumin, Curry (leaf), Dill (dillweed), Dill (seed), Epazote, Fennel seed (common and Florence), Fenugreek, White ginger flower, Grains of paradise, Horehound, Hyssop, Juniper berry, Lavender, Lemongrass, Lovage (leaf and seed), Mace, Marigold, Marjoram (including oregano), Mexican oregano, Mioga flower, Mustard (seed), Nasturtium, Nutmeg, Parsley (dried), Pennyroyal, Pepper (black and white), Pepper leaves, Peppermint, Perilla, Poppy (seed), Rosemary, Rue, Saffron, Sage, Savory (summer and winter), Spearmint, Stevia levas, Sweet bay, Tansy, Tarragon, Thyme, Vanilla, Wintergreen, Woodruff, Wormwood	3.75	1.55	6
Grass/Turfgrass/Sod Production	3.75	1.55	6
Grain Sorghum	3.75	1.55	6
Fruiting Vegetables: Eggplant; Groundcherry (Physalis spp); Pepino; Pepper (includes bell pepper, chili pepper, cooking pepper, pimento, sweet pepper); Tomatillo; Tomato	3.75	1.55	6
Forestry	8	8	8
Fallow	3.75	1.55	6
Cucurbits Vegetables/Fruit: Chayote (fruit); Chinese waxgourd (Chinese preserving melon); Citron melon; Cucumber; Gherkin; Edible gourd (includes hyotan, cucuzza, hechima, Chinese okra); Melons (all); Momordica spp (includes balsam apple, balsam pear, bittermelon, Chinese cucumber); Muskmelon (includes cantaloupe, casaba, crenshaw melon, golden pershaw melon, honeydew melon, honey ball melon, mango melon, Persian melon, pineapple melon, Santa Claus melon, snake melon); Pumpkin; Summer squash	3.75	1.55	6

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
(includes crookneck squash, scallop squash, straightneck squash, vegetable marrow, zucchini); Winter squash (includes butternut squash, calabaza, hubbard squash, acorn squash, spaghetti squash); Watermelon			
Cotton	3.75	1.55	6
Corn (Field, Seed, Silage, Popcorn)	3.75	1.55	6
Conservation Reserve Program	3.75	1.55	6
Citrus Fruit Crop: All cultivars, varieties and/or hybrids of Calamondin; Chironja; Citron; Citrus hybrids; Grapefruit (including Japanese summer); Kumquat; Lemon; Lime (including Australian desert lime, Australian finger lime, Australian round lime, Brown river finger lime, Mount white, New Guinea wild, Russell river, sweet, and Tahiti); Mandarin (including Mediterranean and Satsuma); Orange (all); Pummelo; Tangelo; Tangerine (Mandarin); Tangor; Uniq Fruit (ugli)	3.75	1.55	8
Cereal and Grain Crop: barley, buckwheat, millet, oats, rye, quinoa, teff, teosinte, triticale, wild rice, rice, feed barley, wheat	3.75	1.55	6
Bulb Vegetables: All cultivars, varieties and/or hybrids of Chive (fresh leaves, including Chinese chive); Daylily (bulb); Elegans hosta; Fritillaria (bulb and leaves); Garlic (bulb, including great-headed and serpent garlic); Kurrant, Leek (including lady's and wild leek); Lily (bulb); Onion (including Beltsville bunching, bulb, Chinese bulb, fresh, green, macrostem, pearl, potato bulb, tree tops and Welsh onion tops); Shallot (bulb and fresh leaves)	3.75	1.55	6
Brassica Vegetable: Broccoli; Chinese broccoli (gai lon); Broccoli raab (rapini); Brussels sprouts; Cabbage; Chinese cabbage (bok choy); Chinese cabbage (napa); Chinese mustard cabbage (gai choy); Cauliflower; Cavalo broccoli; Collards; Kale; Kohlrabi; Mizuna; Mustard greens; Mustard spinach; Rape greens	3.75	1.55	6
Round-up Ready Flex Cotton	3.75	1.55	6
Round-up Ready Cotton	3.75	1.55	6
Round-up Ready Corn (GA-21)	3.75	1.55	6
Round-up Ready Corn 2 (NK603)	3.75	1.55	6
Round-up Ready Alfalfa	1.55	1.55	6
Round-up Ready Sugarbeets	3.75	1.55	6
Tropical/Subtropical Trees/Fruits: Ambarella; Atemoya; Avocado; Banana; Barbados cherry (acerola); Biriba; Blimbe; Breadfruit; Cacao (cocoa) bean; Canistel; Carambola (starfruit); Cherimoya; Coffee; Custard apple; Dates; Durian; Feijoa; Figs; Governor's plum; Guava; Ilama; Imbe; Imbu; Jaboticaba; Jackfruit; Longan; Lychee; Mamey apple; Mango; Mangosteen; Marmaladebox (genip); Mountain papaya; Noni	3.75	1.55	8

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
(Indian mulberry); Papaya; Pawpaw; Plantain; Persimmon; Pomegranate; Pulasan; Rambuttan; Rose apple; Sapodilla; Sapote (black, mamey, white); Spanish lime; Soursop; Star apple; Sugar apple; Surinam cherry; Tamarind; Tea; Ti (roots and leaves); Wax jambu			
Tree Nut Crops: Cultivars, varieties, and/or hybrids of African nut-tree; Almond; Beechnut; Brazil nut; Brazilian pine; Bunya; Burr oak; Butternut; Cajou nut; Candlenut; Cashew; Chestnut; Chinquapin; Coconut; Coquito nut; Dika nut; Ginkgo; Guiana chestnut; Hazelnut (Filbert); Heartnut; Hickory nut; Japanese horse-chestnut; Macadamia nut; Mongongo nut; Monkey-pot; Monkey puzzle nut; Okari nut; Pachira nut; Peach palm nut; Pecan; Pequi; Pili nut; Pine nut; Pistachio; Sapucaia nut; Tropical almond; Walnut (black, English); Yellowhorn	3.75	1.55	8
Sweet Corn	3.75	1.55	6
Sugar Cane	3.75	2.25	6
Stone Fruit: All cultivars, varieties and/or hybrids of Apricot; Cherry (sweet and tart); Nectarine; Olive; Peach; Plum/Prune (all types); Plumcot	3.75	1.55	8
Round-Up Ready Canola (Winter Varieties)	1.55	1.55	6
Soybeans	3.75	1.55	6
Sweet Corn with Round-Up Ready 2 Technology	3.75	1.55	6
Round-Up Ready Canola (Spring Varieties)	1.55	1.55	6
Vine Crops: grapes (raisin, table, wine), hops, passion fruit, kiwi	3.75	1.55	8

Crop Group	Ground Maximum Single Application Rate (lb a.e./A)	Aerial Maximum single application rate (lb a.e./A)	Maximum Annual Application Rate (lb a.e./A)
Non-Crop: Airports, airfields, apartment complexes, commercial sites, ditch banks, driveways, ramps, alleys, lanes, paths, trails, sidewalks, walkways, access roads, farm roads, highways (including aprons, medians, guardrails, and rights-of-way), paved areas and prior to paving, dry ditches, dry canals, fences and fencerows, golf courses, greenhouses, industrial sites, landscape areas, lumber yards, manufacturing sites, municipal sites, natural areas, office complexes, ornamentals, parks, campgrounds, sports areas, tennis courts, parking areas, cemeteries, petroleum or other tank farms and pumping installations, refineries, around telephone and communications equipment, public areas, drive-in theaters, railroads (including ballasts, shoulders, crossings and spot treatments), recreation areas, residential areas, rights-of-way, roadsides, firebreaks, schools, shadehouses, sports complexes, storage areas, substations, construction and pre-construction sites, turfgrass areas, around ornamental gardens, around ornamental trees and shrubs, power and utility sites, around commercial or industrial outbuildings, warehouse areas, bare ground, gravel yards, mulched areas, beaches, habitat restoration and management areas, uncropped farmstead areas, uncultivated non-agricultural areas, vacant lots, wastelands, shelter belts, and wildlife management areas. Natural Woodlands, including Wildlife and Habitat Management Areas, Wildlife Openings, Natural Areas (such as Wildlands and Wildlife Refuge), Campgrounds, Parks and Recreational Areas in Natural Forests, and Reforestation Treatments in Natural Forests	8	8	8
Aquatic	8	8	8
Alfalfa, Clover, and Other Forage Legumes, including: kudzu, lespedeza, lupin, sainfoin, trefoil, velvet bean, vetch, kenaf, leucaena	3.75	1.55	6
Berry and Small Fruit Crops: All cultivars, varieties and/or hybrids of Amur River grape; Aronia berry; Bayberry; Bearberry; Bilberry; Blackberry (including Andean blackberry, arctic blackberry, bingleberry, black satin berry, boysenberry, brombeere, California blackberry, Chesterberry, Cherokee blackberry, Cheyenne blackberry, common blackberry, coryberry, darrowberry, dewberry, Dirksen thornless berry, evergreen blackberry, Himalayaberry, hullberry, lavacaberry, loganberry, lowberry, Lucretiaberry, mammoth blackberry, marionberry, mora, mures deronce, nectarberry, Northern dewberry, olallieberry, Orgeon evergreen berry, phenomenalberry, rangeberry, ravenberry, rossberry, Shawnee blackberry, Southern dewberry, tayberry, youngberry, zarzamora); Blueberry (highbush and lowbush); Buffaloberry; Che; Chilean guava; Chokecherry; Cloudberry; Cranberry (including highbush); Currant (black, Buffalo, red, native); Elderberry; European barberry; Gooseberry; Grape; Honeysuckle (edible); Huckleberry; Jostaberry; Juneberry (Saskatoon berry); Kiwifruit (fuzzy and hardy); Ligonberry; Maypop; Mountain pepper berries; Mulberry; Muntries; Partridgeberry; Phalsa; Pincherry; Raspberry (black, red and wild); Riberry; Salal; Schisandra berry; Sea buckthorn; Serviceberry	3.75	1.55	8

Appendix D: Endangered Species Assessment

This Appendix provides general background about the Agency's assessment of risks from pesticides to endangered and threatened (listed) species under the Endangered Species Act. Additional background specific to glyphosate appears at the conclusion of this Appendix.

In 2013, the EPA, along with the Fish and Wildlife Service (FWS), the National Marine Fisheries Service (NMFS), and the United States Department of Agriculture (USDA) released a summary of their joint Interim Approaches for assessing risks to endangered and threatened (listed) species from pesticides⁶. These Interim Approaches were developed jointly by the agencies in response to the National Academy of Sciences' (NAS) recommendations that discussed specific scientific and technical issues related to the development of pesticide risk assessments conducted on federally threatened and endangered species.

Since that time, EPA has conducted biological evaluations (BEs) on three pilot chemicals representing the first nationwide pesticide consultations. These initial consultations were pilots and were envisioned to be the start of an iterative process. The agencies are continuing to work to improve the consultation process. For example, advancements to the initial pilot interim methods have been proposed based on experience conducting the first three pilot BEs. Public input on those proposed revisions is currently being considered.

Also, a provision in the December 2018 Farm Bill included the establishment of a FIFRA Interagency Working Group to provide recommendations for improving the consultation process required under section 7 of the Endangered Species Act for pesticide registration and Registration Review and to increase opportunities for stakeholder input. This group includes representation from EPA, NMFS, FWS, USDA, and the Council on Environmental Quality (CEQ). Given this new law and that the first nationwide pesticide consultations were envisioned as pilots, the agencies are continuing to work collaboratively as consistent with the congressional intent of this new statutory provision. EPA has been tasked with a lead role on this group, and EPA hosted the first Principals Working Group meeting on June 6, 2019.

Given that the agencies are continuing to develop and work toward implementation of approaches to assess the potential risks of pesticides to listed species and their designated critical habitat, the ecological risk assessment supporting this ID for glyphosate does not contain a complete ESA analysis that includes effects determinations for specific listed species or designated critical habitat. Although the EPA has not yet completed effects determinations for specific species or habitats, for this ID, the EPA's evaluation assumed, for all taxa of non-target wildlife and plants, that listed species and designated critical habitats may be present in the vicinity of the application of glyphosate. This will allow the EPA to focus its future evaluations on the types of species where the potential for effects exists once the scientific methods being developed by the agencies have been fully vetted. Once that occurs, these methods will be applied to subsequent analyses for glyphosate as part of completing this registration review.

⁶ <https://www.epa.gov/endangered-species/draft-revised-method-national-level-endangered-species-risk-assessment-process>

Glyphosate is one of the chemicals in stipulated partial settlement agreement in the case of Center for Biological Diversity et al., v. United States Environmental Protection Agency et al., No. 3:11 cv 0293 (N.D. Cal.). Among other provisions, this agreement sets an August 14, 2021, deadline for EPA to complete nationwide ESA section 7(a)(2) effects determination for glyphosate and, as appropriate, request initiation of any ESA section 7(a)(2) consultations with the Services that EPA may determine to be necessary as a result of those effects determinations.

Appendix E: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, the EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, the EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for glyphosate, the EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA § 408(p), glyphosate is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

The EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where the EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, the EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The agency has reviewed all of the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. Glyphosate is on List 1 and the review conclusions are available in the glyphosate public docket (see EPA-HQ-OPP-2009-0361). A second list of chemicals identified for EDSP screening was published on June 14, 2013,⁷ and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit the EPA website.⁸

⁷ See <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074> for the final second list of chemicals.

⁸ <https://www.epa.gov/endocrine-disruption>

In this ID, the EPA is making no human health or environmental safety findings associated with the EDSP screening of glyphosate. Before completing this registration review, the agency will make an EDSP FFDCA § 408(p) determination.

Exhibit 5



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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Response from the Pesticide Re-evaluation Division (PRD) to Comments on the Glyphosate Proposed Interim Decision

DATE: January 16, 2020

FROM: Dana L. Friedman
Chief, Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division

THROUGH: Elissa Reaves, PhD
Acting Director
Pesticide Re-evaluation Division

A handwritten signature in blue ink, appearing to read "Elissa Reaves", is positioned to the right of the "THROUGH:" line.

DOCKET: Glyphosate (EPA-HQ-OPP-2009-0361)

Summary

On May 6, 2019, EPA issued a notice in the Federal Register concerning the opening of a public comment period for the proposed interim decision (PID) for glyphosate. This notice announced the publication of the PID, along with supporting documents, and opened a 60-day public comment period concluding on July 5, 2019. Based on multiple requests to extend the public comment period, the agency extended the comment period for an additional 60 days, which then closed on September 3, 2019. During the comment period, the agency received 283,300 comments. Over 12,000 unique submissions were received from various stakeholders, including glyphosate registrants, grower groups, non-governmental organizations, pesticide industry groups, states, the US Department of Agriculture, and members of the general public. Most comments came from mass mailer campaigns, and approximately 120 unique substantive comments were received from various stakeholders.

Along with the interim registration review decision (ID), the agency is posting this document and the *Glyphosate: Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment* document to address comments received on the PID. Most of the comments received on the PID are substantively the same as comments received during previous glyphosate comment periods on the agency's risk assessments. This document combines comments by topic instead of responding to individual stakeholders and directs the public to

Exhibit 6



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460**

**OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION**

August 7, 2019

Dear Registrant,

We are writing to you concerning label and labeling requirements for products that contain glyphosate.

On July 7, 2017, California listed glyphosate as a substance under Proposition 65¹, based on the International Agency for Research on Cancer's (IARC's) classification of the pesticide as "probably carcinogenic to humans." EPA disagrees with IARC's assessment of glyphosate. EPA scientists have performed an independent evaluation of available data since the IARC classification to reexamine the carcinogenic potential of glyphosate and concluded that glyphosate is "not likely to be carcinogenic to humans." EPA considered a more extensive dataset than IARC, including studies submitted to support registration of glyphosate and studies identified by EPA in the open literature as part of a systematic review. For more detailed information on this evaluation, please see the 2017 Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential². Further, EPA's cancer classification is consistent with other international expert panels and regulatory authorities, including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, European Food Safety Authority, European Chemicals Agency, German Federal Institute for Occupational Safety and Health, New Zealand Environmental Protection Authority, and the Food Safety Commission of Japan.

On February 26, 2018, the United States District Court for the Eastern District of California issued a preliminary injunction enjoining California from enforcing the state warning requirements involving the pesticide glyphosate's carcinogenicity, in part on the basis that the required warning statement is false or misleading³.

Given EPA's determination that glyphosate is "not likely to be carcinogenic to humans," EPA considers the Proposition 65 warning language based on the chemical glyphosate to constitute a false and misleading statement. As such, pesticide products bearing the Proposition 65 warning statement due to the presence of glyphosate are misbranded pursuant to section 2(q)(1)(A) of FIFRA and as such do not meet the requirements of FIFRA. In registering pesticides, EPA must determine that the labeling complies with the requirements of FIFRA including that the product

¹ California's Safe Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65) requires businesses to inform Californians about significant exposures to chemicals that, under the terms of Proposition 65, are believed to cause cancer, birth defects or other reproductive harm. See California Office of Environmental Health Hazard Assessment, "Proposition 65," at <https://oehha.ca.gov/proposition-65>.

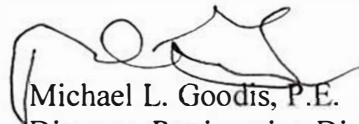
² <https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073>

³ National Association of Wheat Growers, et al. v. Zeise, 309 F.Supp.3d 842 (E.D.Cal.)

not be misbranded. See FIFRA 3(c)(5)(B). Therefore, EPA will no longer approve labeling that includes the Proposition 65 warning statement for glyphosate-containing products. The warning statement must also be removed from all product labels where the only basis for the warning is glyphosate, and from any materials considered labeling under FIFRA for those products.

For any pesticide product that currently contains Proposition 65 warning language exclusively on the basis that it contains glyphosate, EPA requests the submission of draft amended labeling that removes such language within ninety (90) days of the date of this letter.

Sincerely,



Michael L. Goodis, P.E.
Director, Registration Division
Office of Pesticide Programs

Exhibit 7

Final Regulatory Text

Warnings for Exposures to Glyphosate from Consumer Products

Title 27, California Code of Regulations, New Sections 25607.48 and 25607.49
Article 6 Clear and Reasonable Warnings

Section 25607.48 Warnings for Exposures to Glyphosate from Consumer Products – Methods of Transmission.

(a) A warning for exposures to glyphosate from consumer products meets the requirements of this subarticle if it complies with the content requirements in Section 25607.49 and is provided using one or more of the methods listed in Section 25602.

NOTE: Authority cited: Section 25249.12, Health and Safety Code. Reference: Section 25249.6, Health and Safety Code.

Section 25607.49 Warnings for Exposures to Glyphosate from Consumer Products – Content.

(a) A warning for exposures to glyphosate from consumer products meets the requirements of this subarticle if it is provided using the methods required in Section 25607.48 and includes all the following elements:

(1) The symbol required in Section 25603(a)(1).

(2) The words “**CALIFORNIA PROPOSITION 65 WARNING**” in all capital letters and bold print.

(3) The words, “Using this product can expose you to glyphosate. The International Agency for Research on Cancer classified glyphosate as probably carcinogenic to humans. US EPA has determined that glyphosate is not likely to be carcinogenic to humans; other authorities have made similar determinations. A wide variety of factors affect your potential risk, including the level and duration of exposure to the chemical. For more information, including ways to reduce your exposure, go to www.P65Warnings.ca.gov/glyphosate.”

(b) Notwithstanding subsection (a), and pursuant to Section 25603(d), where the warning is provided on the product label, and the label is regulated by the United States Environmental Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act, Title 40 Code of Federal Regulations, Part 156; and by the California Department of Pesticide Regulation under Food and Agricultural Code section 14005,

and Cal. Code of Regs., title 3, section 6242; the word "ATTENTION" or "NOTICE" in capital letters and bold type may be substituted for the words "CALIFORNIA PROPOSITION 65 WARNING".

NOTE: Authority cited: Section 25249.12, Health and Safety Code. Reference: Sections 25249.6 and 25249.11, Health and Safety Code.

Exhibit 8

November 14, 2022

The Honorable Nancy Pelosi
Speaker of the House
United States House of Representatives
H-232, The Capitol
Washington, D.C. 20515

The Honorable Chuck Schumer
Majority Leader
United States Senate
S-221, The Capitol
Washington, D.C. 20510

The Honorable Kevin McCarthy
Minority Leader
United States House of Representatives
H-204, The Capitol
Washington, D.C. 20515

The Honorable Mitch McConnell
Minority Leader
United States Senate
S-230, The Capitol
Washington, D.C. 20510

Dear Speaker Pelosi, Leader Schumer, Leader McCarthy, and Leader McConnell,

We write to express our great concern with recent misinterpretations of long-standing policy regarding the regulation and labeling of pesticide products, as some states have begun to regulate pesticides in a manner contradicting decades of scientific guidance from the Environmental Protection Agency (EPA). Lack of certainty on EPA-approved, science-based nationwide labels will erode access to current and future pesticides, threatening crops and grower incomes, conservation practices, public health, vital infrastructure, and ultimately raise food prices for families amidst record-high inflation. Growers and users need reaffirmation from Congress that states have every right to build on the federal government's baseline regulations but *cannot* directly contradict the scientific conclusions of the EPA.

The last several years have demonstrated how fragile our food production and infrastructure systems can be. Whether driven by war in Ukraine, extreme weather events, or COVID-19 disruptions, our economic wellbeing and access to a safe, affordable food supply relies on many factors. Pesticides are an essential tool for many growers and other users whose operations rely on them, and for consumers and our environment which benefit from their use. If left unchecked, some pests can inflict crop yield losses greater than 80 percent, destroy important infrastructure, harm public health through mosquito-borne disease or other outbreaks, among other harms. Additionally, pesticides are essential to maintaining and expanding vital conservation practices, such as cover crops or tillage reductions, which remove the equivalent of millions of cars from roadways annually, reduce soil erosion, and prevent nutrient loss to watersheds. Without access to safe, effective pesticides regulated with the best available science, food prices for American families will rise significantly and our ability to protect public health, infrastructure, and our environment will be greatly diminished.

Disturbingly, we are seeing in states an emerging threat that risks access to these essential tools on which farmers and other users rely. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the primary statute governing pesticides, places EPA in the authority to make foundational, science-based decisions on how pesticides can be labeled and used. States are permitted to regulate the sale and use of pesticides under FIFRA but are preempted from requiring additional or different pesticide labels or packaging. Nevertheless, in recent years we have seen actions from states that directly and unjustifiably contradict EPA's scientific findings on pesticide safety. These actions risk creating an unworkable, inconsistent patchwork of state or municipal pesticide labels that can quickly disrupt commerce and access to these much-needed tools. As concerning, this threatens to jeopardize public confidence in EPA's authority

and science-based regulation under FIFRA, as well as the continued availability of individual tools on which there are contradictory claims.

We urge Congress to seriously consider the far-reaching implications should this tension go unaddressed by federal policymakers. The ability of farmers, land managers, and other users to produce an abundant food, feed, and fiber supply, combat public health threats, implement important conservation practices, and maintain vital transportation and utility infrastructure will be significantly impaired. In turn, food prices will further increase for families; important infrastructure will fall into disrepair; our population will be increasingly vulnerable to vector-borne diseases; and our ability to combat climate change and other environmental challenges will be undermined. We strongly urge Congress to reaffirm that EPA is the primary, federal authority under FIFRA for making pesticide findings and decisions, and that states may regulate their use, but not impose additional labeling or packaging requirements. Congressional action on this important matter will ensure our nation's farmers and other users have reliable access to these vital tools in the years to come.

Sincerely,

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Agricultural Council of Arkansas
Agricultural Council of California
Agricultural Retailers Association
Alabama Agribusiness Council
Alabama Farmers Federation
Alabama Soybean & Corn Association
Alaska Farm Bureau
Almond Alliance of California
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American Seed Trade Association
American Society of Agronomy
American Soybean Association
American Sugar Alliance
American Sugarbeet Growers Association
AmericanHort
Aquatic Ecosystem Restoration Foundation
Aquatic Plant Management Society
Arizona Farm Bureau
Arkansas Farm Bureau Federation
Arkansas Rice Growers Association
Arkansas Soybean Association
Association of Equipment Manufacturers
California Alfalfa & Forage Association
California Association of Wheat Growers
California Association of Winegrape Growers
California Cattlemen's Association
California Cherry Growers and Industry Association
California Citrus Mutual

California Citrus Quality Council
California Cotton Ginner & Growers Association
California Farm Bureau
California Fresh Fruit Association
California Grain and Feed Association
California Pear Growers Association
California Seed Association
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California State Floral Association
California Sweetpotato Council
California Warehouse Association
California Women for Agriculture
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Corn Refiners Association
Cotton Warehouse Association of America
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Wyoming Ag Business Association
Wyoming Farm Bureau

Exhibit 9

November 14, 2022

The Honorable Nancy Pelosi
Speaker of the House
United States House of Representatives
H-232, The Capitol
Washington, D.C. 20515

The Honorable Chuck Schumer
Majority Leader
United States Senate
S-221, The Capitol
Washington, D.C. 20510

The Honorable Kevin McCarthy
Minority Leader
United States House of Representatives
H-204, The Capitol
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Exhibit 10



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

OFFICE OF CHEMICAL
SAFETY AND POLLUTION PREVENTION

September 21, 2022

MEMORANDUM

SUBJECT: Withdrawal of the *Glyphosate Interim Registration Review Decision*

TO: Glyphosate Registration Review Docket (EPA-HQ-OPP-2009-0361)

FROM: Cathryn Britton, Branch Chief 
Risk Management and Implementation Branch V
Pesticide Re-evaluation Division

THRU: Mary Elissa Reaves, Director 
Pesticide Re-evaluation Division
Office of Pesticide Programs

On June 17, 2022, the United States Court of Appeals for the Ninth Circuit vacated and remanded the human health portion of EPA's interim registration review decision for glyphosate (ID), held that EPA's failure to make an effects determination before issuing the ID violated the Endangered Species Act (ESA), and remanded without vacating the ecological portion of the ID but imposed an October 1, 2022 deadline for EPA to complete the remand. *Natural Resources Defense Council et al. v. EPA*, 38 F.4th 34 (9th Cir. 2022). In light of the court's decision, this memorandum announces EPA's withdrawal of all remaining portions of the glyphosate ID, including the remanded ecological portion.

A copy of the glyphosate ID, now vacated in part and the remainder withdrawn, is posted to the glyphosate registration review public docket (EPA-HQ-OPP-2009-0361) at <https://www.regulations.gov>.

Background

Issuance of the Glyphosate Interim Registration Review Decision

Registration review is EPA's periodic review of pesticide registrations to ensure that each pesticide registration continues to satisfy the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration, that is, that the pesticide can perform its intended function without unreasonable adverse effects on human health or the environment. Under FIFRA section 3(g), each pesticide is required to be reviewed every 15 years.

EPA regulations establish procedures for the registration review program required in FIFRA section 3(g). Under 40 C.F.R. § 155.56, EPA may issue, when it determines it to be appropriate, an interim registration review decision before completing a registration review. Among other things, the interim registration review decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment, and completing the registration review. Procedures for issuing an interim registration review decision are set forth in § 155.58.

On February 3, 2020, EPA published a notice in the Federal Register (85 Fed. Reg. 5957) announcing the availability of the glyphosate ID. EPA issued the ID pursuant to 40 C.F.R. §§ 155.56 and 155.58, explaining that it was doing so to “(1) move forward with aspects of the registration review case that are complete and (2) implement interim risk mitigation.” The ID finalized EPA’s draft risk assessments supporting registration review, *Glyphosate Draft Human Health Risk Assessment for Registration Review and Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*. The ID did not identify any human health risks of concern from exposure to glyphosate but did identify potential ecological risks. It also identified interim risk mitigation measures, in the form of label changes, including spray drift management language, herbicide resistance management language, a non-target organism advisory, and certain label consistency measures. It concluded that, under FIFRA, the benefits of glyphosate outweigh the potential ecological risks when glyphosate is used in accordance with labels.

The glyphosate ID did not make findings under section 7 of the ESA or under the Endocrine Disruptor Screening Program (EDSP) pursuant to section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA), nor did it respond to a 2018 administrative petition submitted by the Environmental Working Group and others (EWG et al.) to reduce the tolerance level for glyphosate residues on oats and require certain label changes based on concerns regarding dietary exposure and carcinogenicity. EPA explained that it would do so before completing registration review for glyphosate, and that the “final registration review decision for glyphosate will be dependent upon the result of the agency’s ESA assessment and any needed section 7 consultation with the [U.S. Fish and Wildlife Service and the National Marine Fisheries Service], an EDSP FFDCA section 408(p) determination, and after a resolution of the EWG et al. petition.” The glyphosate ID also did not solicit label changes from registrants to implement the interim risk mitigation measures. EPA explained that it would do so once it responded to the EWG et al. petition.

For further background on glyphosate and its registration review history, see the end of this memorandum.

Endangered Species Act Assessment for Glyphosate

ESA section 7(a)(2) requires that federal agencies ensure that the actions they authorize, fund, or carry out are not likely to jeopardize the continued existence of species listed as

threatened or endangered under the ESA (listed species) or destroy or adversely modify their designated critical habitat. For pesticides in registration review, EPA's responsibility includes evaluating potential effects to listed species and their designated critical habitat, often through a biological evaluation (BE). If EPA determines that a pesticide's registration "may affect" and is "likely to adversely affect" listed species or designated critical habitat, the Agency initiates formal consultation with the U.S. Fish and Wildlife Service (FWS) and/or the National Marine Fisheries Service (NMFS) (together, the Services). The Services prepare their respective biological opinions (BiOps) regarding whether the pesticide's registration is likely to jeopardize the continued existence of listed species or result in the destruction or adverse modification of designated critical habitats and describing any reasonable and prudent measures or reasonable and prudent alternatives. EPA then uses its authorities under FIFRA to implement, as necessary, any such measures or alternatives described in the BiOps.

On November 25, 2020, EPA released the draft BE for glyphosate for public comment. On November 12, 2021, EPA released the final BE for glyphosate, which found that glyphosate may affect 1,795 listed species and 792 critical habitats and is likely to adversely affect 1,676 of those species and 759 of those habitats. EPA initiated formal consultation with the Services in November 2021. As noted in the declaration filed in support of EPA's August 1, 2022 petition for panel rehearing of the Ninth Circuit's decision, discussed below, consultation with the Services is ongoing.

For further information on EPA's ESA assessment for glyphosate, see <https://www.epa.gov/endangered-species/final-national-level-listed-species-biological-evaluation-glyphosate>.

Challenges to Glyphosate Interim Registration Review Decision

On March 20, 2020, two groups of petitioners filed petitions for review of the glyphosate ID in the Ninth Circuit. See *Natural Resources Defense Council et al. v. EPA*, No. 20-70787 and *Rural Coalition et al. v. EPA*, No. 20-70801. Together these petitions challenged EPA's analysis of the human health and ecological risks and costs of glyphosate, weighing of such risks against the benefits of glyphosate, and the interim risk mitigation measures identified in the ID, and alleged that EPA violated the ESA by issuing the ID before completing consultation with the Services.

While EPA defended its analysis of human health risks and the alleged ESA violation, it moved for partial voluntary remand without vacatur of its analysis of ecological risks and costs, weighing of such risks against benefits, and interim risk mitigation measures. EPA sought remand to:

- Consider how the glyphosate ID may be impacted by the (then) draft BE and whether additional or different risk mitigation measures may be necessary.
- Reconsider its analysis of ecological risks as it relates to in-field effects of glyphosate on monarch butterfly habitat in light of the court decision in *National Family Farm Coalition v. EPA*, 966 F.3d 893 (9th Cir. 2020).

- Consider whether the court decision in *National Family Farm Coalition v. EPA*, 960 F.3d 1120 (9th Cir. 2020) regarding EPA’s analysis of spray drift risks and other potential costs of another pesticide (dicamba) affected EPA’s analysis of glyphosate.
- Evaluate the glyphosate ID in light of the change in Administration and policy priorities, as reflected in the January 20, 2021 “Executive Order on Protecting Public Health and the Environment and Restoring Science to Tackle the Climate Crisis” (86 FR 7037, 1/25/21) and, in particular, consider whether there are other aspects of its analysis of ecological risks and costs related to glyphosate that should be reassessed or for which additional explanation should be provided.
- Consider what risk mitigation measures may be necessary to reduce potential risks following completion of analyses left outstanding in the ID.

The Ninth Circuit heard oral argument on these challenges on January 10, 2022 and issued its decision on June 17, 2022. The court vacated and remanded the human health portion of the glyphosate ID, held that EPA’s failure to make an effects determination before issuing the ID violated the ESA, and granted EPA’s motion for partial voluntary remand but imposed an October 1, 2022 deadline for EPA “to issue a new ecological portion.” *Natural Resources Defense Council et al. v. EPA*, 38 F.4th 34 (9th Cir. 2022).

On August 1, 2022, EPA filed a petition for panel rehearing that sought relief only from the court’s imposition of a deadline to complete remand of the ecological portion of the ID. EPA explained that, while the court did not define what it meant by “issue a new ecological portion,” the Agency would not be able to finalize a new ecological portion in a registration review decision for glyphosate by the October 1, 2022 deadline because of the time needed to address the issues for which EPA sought remand and to complete consultation under the ESA. In a declaration filed in support of the petition, EPA set forth its anticipated schedule for completing registration review for glyphosate. EPA also stated that if the court did not lift the deadline, the Agency might exercise its discretion to withdraw the remanded ecological portion of the ID and focus its efforts on the required final registration review decision for glyphosate. A copy of EPA’s August 1, 2022 petition for panel rehearing and declaration filed in support of the petition is posted to the glyphosate registration review public docket (EPA-HQ-OPP-2009-0361) at <https://www.regulations.gov>.

On August 5, 2022, the court denied EPA’s petition for panel rehearing without opinion.

Withdrawal

In its June 17, 2022 decision, the Ninth Circuit vacated and remanded the human health portion of the glyphosate ID. EPA is now withdrawing all remaining portions of the ID, including the remanded ecological portion consisting of the Agency’s analysis of the ecological risks and costs of glyphosate, the weighing of such risks against the benefits of glyphosate, and interim risk mitigation measures. Because the ID is an informal adjudication that EPA issued at its discretion, EPA may withdraw all or a portion of it without public comment. Moreover, it would be impracticable for EPA to take public

comment here because of the October 1, 2022 deadline imposed by the court to complete remand of the ecological portion of the ID.

EPA has determined that withdrawal is appropriate in light of the Ninth Circuit’s June 17, 2022 decision and the particular circumstances of glyphosate’s registration review and ESA assessment. Insofar as the court has ordered EPA to finalize a “new ecological portion,” doing so through another interim registration review decision or a final registration review decision would involve significant and lengthy steps. As detailed in EPA’s August 1, 2022 petition for panel rehearing and declaration filed in support of the petition, the Agency is unable to finalize a new ecological portion in a registration review decision for glyphosate by the court-imposed October 1, 2022 deadline because of the time needed to address the issues for which EPA sought remand and to complete consultation under ESA. Moreover, before issuing such a decision, EPA must first prepare a proposed decision, make it available for a period of public comment of at least 60 days, and consider any comments received. 40 C.F.R. § 155.58. For reference, EPA received approximately 283,300 public comments comprising over 12,000 unique submissions when it published the glyphosate proposed ID in May 2019, and it then took nine months to finalize and publish the ID in February 2020. EPA cannot complete these processes by the court-imposed October 1, 2022 deadline.

To date, EPA has not solicited label changes from registrants to implement the interim risk mitigation measures identified in the ID. The Agency has not solicited such label changes because EPA’s continued work towards completing registration review for glyphosate could affect what risk mitigation measures EPA may determine are necessary, as noted in the declaration filed in support of EPA’s August 1, 2022 petition for panel rehearing of the Ninth Circuit’s decision. Moreover, the Agency continues to work on a response to the EWG et al. petition, which asks EPA to reduce the tolerance level for glyphosate residues on oats and require certain label changes based on concerns regarding dietary exposure and carcinogenicity. Because of the court’s vacatur and remand of the human health portion of the ID, EPA believes it would be appropriate to respond to the EWG et al. petition once it completes its review on remand. To avoid multiple, and potentially conflicting, rounds of label changes, EPA expects to defer solicitation of label changes until it issues a final registration review decision for glyphosate.

For these reasons, EPA believes it is appropriate to withdraw all remaining portions of the glyphosate ID, including the remanded ecological portion, and focus its efforts on completing the required final registration review decision for glyphosate.

Although the glyphosate ID is now vacated in part and the remainder withdrawn, that does not automatically mean that EPA’s underlying scientific findings regarding glyphosate, including its finding that glyphosate is not likely to be carcinogenic to humans, are either incorrect or cannot be used as support for a future decision following reconsideration in accordance with the court’s decision.

Next Steps

With respect to the vacated human health portion of the ID, in accordance with the Ninth Circuit's June 17, 2022 decision, EPA intends to revisit and better explain its evaluation of the carcinogenic potential of glyphosate and to consider whether to do so for other aspects of its human health analysis. With respect to the withdrawn ecological portion of the ID, EPA intends to address the issues for which it sought remand, including:

- Consider whether additional or different risk mitigation measures may be necessary based on the outcome of ESA consultation for glyphosate.
- Prepare an analysis of in-field effects of glyphosate on monarch butterfly habitat.
- Consider whether EPA's analysis of spray drift risks and other potential costs of dicamba are relevant to EPA's analysis of glyphosate's risk from spray drift.
- Consider whether there are other aspects of EPA's analysis of ecological risks and costs related to glyphosate that should be reassessed or for which additional explanation should be provided.
- Consider what risk mitigation measures may be necessary to reduce potential risks following completion of analyses left outstanding in the ID.

EPA also intends to complete ESA consultation with the Services, respond to the EWG et al. petition, and make an FFDCA section 408(p) EDSP determination before issuing a final registration review decision for glyphosate. As noted in the declaration filed in support of EPA's August 1, 2022 petition for panel rehearing of the Ninth Circuit's decision, EPA anticipates issuing a final registration review decision for glyphosate in 2026.

Glyphosate Background and Registration Review History

Glyphosate is a non-selective, systemic herbicide with products registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, cereal grains, and other field crops. Non-agricultural uses include residential spot treatments, aquatic areas, forests, rights-of-way, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land. Glyphosate products are also registered for use on the glyphosate-resistant crops, including alfalfa, corn, soybean, cotton, canola, and sugar beets.

EPA formally initiated registration review for glyphosate in 2009 with the opening of the registration review docket for the case. The following summary highlights significant milestones that have occurred during the registration review of glyphosate

- July 2009 - The *Glyphosate Preliminary Work Plan (PWP)*, the *Glyphosate Human-Health Assessment Scoping Document in Support of Registration Review*, and the *Registration Review–Preliminary Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments for Glyphosate and Its Salts* were posted to the docket for a 60-day public comment period.

- December 2009 - The *Glyphosate Final Work Plan (FWP)* was issued. Comments received on the PWP covered the following topics: opposition to the use of glyphosate, the toxicity of glyphosate formulations and inert ingredients, use and usage trends, human health risks, ecological risks, endocrine disruption, and the benefits of glyphosate. The public comments received did not change the schedule, risk assessment needs, or anticipated data requirements in the FWP.
- September 2010 - A Generic Data Call-In (GDCI) for glyphosate was issued for data needed to conduct the registration review risk assessments. All required data were submitted and reviewed. The registration review GDCI for glyphosate is considered satisfied.
- September 2015 – The Agency completed its evaluation of Tier 1 endocrine data submitted under the EDSP and published the *Glyphosate: Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen, or Thyroid Pathways*. EPA found no convincing evidence of potential interaction with the estrogen, androgen, or thyroid pathways and glyphosate was not recommended for further EDSP testing.
- December 2016 – The agency convened a FIFRA Scientific Advisory Panel meeting to consider and review a set of scientific issues related to the EPA’s evaluation of the carcinogenic potential of glyphosate. The meeting agenda, the agency’s cancer issue paper, charge questions for the panel, transcript, and final report are available on EPA’s website: <https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel>. Additional supporting materials and comments received from the public can be found in docket EPA-HQ-OPP-2016-0385 at www.regulations.gov.
- December 2017 – The agency published the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (dated December 12, 2017), the *Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate* (dated December 12, 2017), the *Glyphosate Draft Human Health Risk Assessment for Registration Review* (dated December 12, 2017), and the *Registration Review – Preliminary Ecological Risk Assessment for Glyphosate and its Salts* (dated September 8, 2015) on EPA’s website: <https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate>.
- February 2018 - The agency announced the availability of the human health and ecological risk assessments for a 60-day public comment period. Over 238,000 comments were received during the comment period, most of which came from various mass mail campaigns. Approximately 2,244 unique submissions were received from various stakeholders, including pesticide registrants, industry groups, farmers, grower groups, private citizens, non-governmental organizations, states, and the U.S. Department of Agriculture. The comments did not change the risk assessments or registration review timeline for glyphosate.

- September 2018 – The Environmental Working Group, joined by Ben & Jerry’s Homemade, Inc., Happy Family Organics, MegaFood, MOM’s Organic Market, National Co+op Grocers, Nature’s Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farm, Inc. submitted an administrative petition to the Agency. The petition requested that EPA lower the tolerance for residues of glyphosate on oats and require label changes to prohibit the preharvest use of glyphosate on oats. On May 6, 2019, the Agency published a Notice of Filing of the petition in the Federal Register for a 30-day public comment period in docket EPA-HQ-OPP-2019-0066. 103,447 comments were received on the petition, most of which came from mass mail campaigns and 419 of which represented unique comments. The Agency continues to work on its response to the petition.
- May 2019 - The Agency announced the availability of the *Glyphosate Proposed Interim Registration Review Decision* (PID) for a 60-day public comment period, which was later extended to 120 days. Along with the PID, the following documents were posted to the docket:
 - *Glyphosate: Response to Comments, Usage, and Benefits* (dated April 18, 2018)
 - *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* (dated April 23, 2019)
 - *Response to Public Comments on the Preliminary Ecological Risk Assessment for Glyphosate* (dated November 21, 2018)

During the 120-day comment period on the PID, the agency received roughly 283,300 comments. Over 12,000 unique submissions were received from various stakeholders, including glyphosate registrants, grower groups, non-governmental organizations, pesticide industry groups, states, the U.S. Department of Agriculture and members of the general public. Most comments came from mass mailer campaigns, and approximately 120 unique substantive comments were received from various stakeholders. Public comments did not change the Agency’s risk conclusions but resulted in changes to the spray drift management labeling and rotational crop instructions.

- February 2020 – The Agency announced the availability of the ID. Along with the ID, the following documents were published in the docket:
 - *Response from the Pesticide Reevaluation Division to Comments on the Glyphosate Proposed Interim Decision* (dated January 16, 2020)
 - *Glyphosate Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment* (dated January 13, 2019)
 - *Glyphosate: Epidemiological Review of Zhang et al. (2019) and Leon et al. (2019) publications for Response to Comments on the Proposed Interim Decision* (dated January 6, 2020)
- November 2020 - The Agency released the draft BE for glyphosate for public comment. Approximately 870 comments that pertained to the draft BE for

glyphosate were submitted, including 11 requests for extensions of the public comment period. Additionally, six mass mail campaigns were submitted with approximately 110,000 signatures.

- November 2021 - The Agency released the final BE for glyphosate evaluating potential effects to listed species and critical habitats.

Exhibit 11



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: January 6, 2020

SUBJECT: **Glyphosate:** Epidemiology Review of Zhang et al. (2019) and Leon et al. (2019) publications for Response to Comments on the Proposed Interim Decision

PC Code: 417300; 103601; 103603; 103604; 103605; 103607;
103608; 103613

Decision No.: 558081

Petition No.: NA

Risk Assessment Type: NA

TXR No.: NA

MRID No.: NA

DP Barcode: D455531

Registration No.: NA

Regulatory Action: Registration Review

Case No.: 178

CAS No.: 1071-83-6; 38641-94-0; 70393-85-0; 114370-14-8;
40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1

40 CFR: §180.364

FROM: David J. Miller, Acting Chief
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

TO: Christine Olinger, Chief
Risk Assessment Branch I
Health Effects Division (7509P)

Glyphosate is currently undergoing Registration Review. As part of the public comment period on the preliminary interim decision (PID) to support Registration Review, open literature studies were identified for the Agency's consideration. Of these, HED's RAB I has requested that TEB review and evaluate two recent review articles involving meta-analyses that were recently published in the scientific literature in 2019. These are:

- **Zhang et al. (2019). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. *Mutation Research/Reviews in Mutation Research* 781:186-206. doi: 10.1016/j.mrrev.2019.02.001.**
- **Leon et al. (2019). Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway, and the USA: a pooled analysis from the AGRICOH consortium. *Int J. Epidemiol.* 48(5):1519-1535. doi: 10.1093/ije/dyz017.**

These summary articles, importantly, both incorporate a recent update on glyphosate and non-Hodgkin's Lymphoma (NHL) published as part of the Agricultural Health Study (AHS) (Andreotti, G., Koutros, S., Hofmann, J.N., Sandler, D.P., Lubin, J.H., Lynch, C.F., Lerro, C.C., De Roos, A.J., Parks, C.G., Alavanja, M.C., Silverman, D.T. 2018. Glyphosate use and cancer incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute*. doi:10.1093/jnci/djx233). This 2018 AHS publication was previously reviewed by TEB under separate cover (A. Aldridge, DP Barcode D444727, 12/12/2017)¹.

This memorandum provides review and comments on the above two referenced summary review articles to ensure that these are appropriately considered as part of Registration Review for glyphosate. The memorandum is divided into two parts, the first of which covers Zhang et al. (2019) and the second which covers Leon et al. (2019).

PART I. Review of Zhang et al. (2019)

Zhang et al. (2019). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. Mutation Research/Reviews in Mutation Research.
<https://doi.org/10.1016/j.mrrev.2019.02.001>

This review article summarizes epidemiologic studies published through 2018² on the association between exposure to glyphosate and NHL. The authors conducted meta-analyses for the epidemiological studies using an *a priori* hypothesis that the highest exposures to glyphosate-based herbicides (GBHs) will lead to increased risk of NHL in humans. Here, higher exposures corresponded to higher levels, longer durations, and sufficient lags/latencies. Additionally, the article provides a summary of lymphoma prevalence in laboratory animals and cites possible mechanisms, including as immunosuppression, endocrine disruption, genetic alterations, and oxidative stress. This memorandum considers only the epidemiological and meta-analysis content of the Zhang et al (2019) publication and does not review or otherwise evaluate the cited putative mechanisms.

The authors began by conducting their own literature search and identified a total of 909 articles using PRISMA guidelines³, with 857 of the articles identified through PubMed and 52 through review of the (previously published) US EPA, International Agency for Research on Cancer (IARC), and Joint Meeting on Pesticide Residues (JMPPR) reviews and reports. After removing duplicates (n=43) and excluding 850 studies which were either not relevant (animal, para-occupational, or mechanistic studies) or were otherwise inappropriate (generally reports, correspondence, reviews, or documents that did not include the exposure or outcome of interest), a total of 16 full-text articles were assessed. Of these 16, a total of 10 were excluded due to the lack of a risk estimate (n=3), it being an overlapping study (n=6), or containing an uncertain NHL diagnosis (n=1), leaving a total of 6 studies to be included in the meta-analysis. These six studies were the same as the six studies included in the Agency's evaluation of the human carcinogenic potential of glyphosate that was presented to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in 2016.⁴ These six articles are listed below:

¹ Review available at <https://beta.regulations.gov/document/EPA-HQ-OPP-2009-0361-0074>

² The article does not indicate when the search years began, but indicated the literature search was done initially in November 2017 and then updated in March 2018 and then again in August 2018.

³ D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, and P. Group. *Preferred reporting items for systematic review and meta-analysis, the PRISMA Statement*, 2009. *PLoS Med* 6 e1000097.

⁴ See <https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel>

- (1) McDuffie, H.H., Pahwa, P., McLaughlin, J.R., Spinelli, J.J., Fincham, S., Dosman, J.A., Robson, D., Skinnider, L.F., and Choi, N.W. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. *Cancer Epidemiol. Biomarkers Prev* 10(11): 1155-1163.
- (2) Hardell, L., Eriksson, M., and Nordstrom, M. (2002). Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma*. 2002 May;43(5):1043-1049.
- (3) De Roos, A.J., Zahm, S.H., Cantor, K.P., Weisenburger, D.D., Holmes, F.F., Burmeister, L.F., and Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occupational and environmental medicine* 60(9): 1-9. doi: 10.1136/oem.60.9.e11.
- (4) De Roos, A.J., Blair, A., Rusiecki, J.A., Hoppin, J.A., Svec, M., Dosemeci M., Sandler D.P., Alavanja, M.C. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 113(1): 49-54.
- (5) Eriksson, M., Hardell, L., Carlberg, M., and Akerman, M. (2008). Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *International journal of cancer* 123(7):1657-1663. doi: 10.1002/ijc.23589.
- (6) Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Marit, G., Soubeyran, P., Huguot, F., Milpied, N., Leporrier, M., Hemon, D., Troussard, X., and Clavel, J. (2009). Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occupational and environmental medicine* 66(5): 291-298.

In addition, the Zhang et al. (2019) authors identified a (then) recent publication on the AHS with updated cohort data for glyphosate and NHL (Andreotti et al., 2018):

Andreotti, G., et al. (2018). Glyphosate use and cancer incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute* 110(5): 509–516. doi:10.1093/jnci/djx233

An earlier AHS publication (De Roos et al., 2005) was considered in the 2016 SAP evaluation and followed that AHS cohort from enrollment in 1993-1997 to December 31, 2001. Andreotti et al. (2018) provides a (post-2016 SAP) AHS update to this publication with an extended follow-up period through 2012/2013 and adds a much larger number of cases. Specifically, the Andreotti et al. (2018) publication updates and supersedes the 2005 De Roos AHS publication and adds 11-12 additional years of follow-up data and considered over five times as many NHL cases (n=575 rather than n=92). TEB prepared an independent review of this AHS study after the 2016 SAP when this publication appeared summarizing the findings (A. Aldridge, DP Barcode D444727, 12/12/2017)⁵. In addition, Andreotti et al. (2018) was also included and addressed in EPA's Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential (DP Barcode D444689, TXR# 0057688, 12/12/2017)⁶ which updated the issue paper presented to the FIFRA SAP in 2016. Specifically, the EPA's Revised Glyphosate Issue Paper addressed comments raised by the SAP and incorporated the aforementioned TEB review of Andreotti et al. (2018). Thus, all the data/information summarized and re-interpreted by the Zhang et al. (2019) article have been previously considered by EPA.

⁵ Review available at <https://beta.regulations.gov/document/EPA-HQ-OPP-2009-0361-0074>

⁶ See https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=OPP&dirEntryId=337935

The six retained studies retained by the Zhang et al (2019) authors were evaluated, along with the recent AHS updated by Andreotti et al (2018), by quality scores using the Newcastle-Ottawa Scale (NOS)⁷ with the two highest scoring studies (7 or 8 points) being the prospective cohort AHS studies (Andreotti et al. (2018) and its progenitor study DeRoos et al. (2005)) and Eriksson et al. (2008), a case-control study. The remaining studies scored either 6 points or 2 points by the NOS, with this latter low score applying only to a case-control study by Orsi et al. (2009). These ratings coincide with the rankings given by EPA in our December 2017 Revised Glyphosate Issue Paper, which ranked De Roos et al. (2005) and Eriksson et al. (2008) as high quality and the remaining four as moderate quality.

Zhang et al (2019) concluded based on their current meta-analysis of human epidemiological studies, using their *a priori* hypothesis that those with higher exposures to GBH will show increased risks of NHL, that GBH exposure was associated with increased risk of NHL in humans. Using the highest cumulative exposures reported, they emphasized in their review article a meta-risk ratio (mRR) of 1.41 (95% CI: 1.13-1.75) using a fixed effect model which included the most recent (Andreotti, 2018) AHS study. They compared this to a mRR estimate of 1.45 (95% CI: 1.11, 1.91) for the fixed effect model using the earlier AHS study (DeRoos et al., 2005) study in place of Andreotti (2019). They reported that a number of sensitivity analyses performed did not reveal substantively different results and concluded that “our current meta-analysis of human epidemiological studies suggests a compelling link between exposures to GBHs and increased risk for NHL.”

TEB Evaluation of Zhang et al (2019) Review

TEB was asked to provide an evaluation of the epidemiological summary and meta-analysis performed by Zhang et al (2019) and to update the prior meta-analysis done for our EPA December 2017 Revised Glyphosate Issue Paper. We do this below in two parts: (i) a commentary on the Zhang et al. (2019) review and (ii) a re-analysis/update of the high and moderate quality studies investigating NHL selected by EPA previously, substituting the more recent Andreotti et al. (2018) AHS results for the earlier De Roos et al (2005) results.

(i) TEB Commentary on Zhang et al (2019) Review

As stated above, Zhang et al (2019) performed a meta-analysis of human epidemiological studies to evaluate the *a priori* hypothesis that higher and longer cumulative GBH exposure are likely to yield higher NHL risk estimates than lower and shorter exposures. They reported, depending on the model used, that exposure to glyphosate is associated with a roughly 40 to 60% increase in the incidence of NHL. TEB offers the following points with respect to their analysis:

- Zhang et al (2019) focused their conclusions on the results from a fixed effect meta-analysis on the highest exposure categories presented in each article, including Andreotti et al. (2018). They state that the use of the fixed effect inverse variance method assigns weights to each study that are directly proportional to the study precision which (they appear to believe) is superior to a random effects model where weights are “based on a complex mix of study precision, relative risk (RR), and meta-analysis size.” They continue, stating that

“One benefit of the random effects model is the ability to incorporate between study variance into the summary variance estimate and confidence intervals which may help prevent artificially narrow confidence intervals resulting from use of the fixed effects model in the presence of between study heterogeneity. However, a feature of the random effects model is that study weighting is not directly

⁷ G. Wells, B. Shea, D. O’Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-randomized Studies in Meta-Analysis. Ottawa Hospital Research Institute. Ottawa (ON 2009). Available March 2016.

proportional to study precision, and greater relative weight is given to smaller studies which may result in summary estimates that are less conservative than the fixed effects model”

The use of a fixed effect meta-analysis (instead of random) for this kind of data is unusual and the rationale used by the Zhang et al. (2019) authors to justify this use is incorrect. The authors did present the results from the correct (random effects) model but indicated in their publication that they were not emphasizing them.⁸ While the results of the random effects model are not substantively different from the fixed effects model (they reported a mRR of 1.56 (95% CI: 1.12, 2.16) using a random effects model incorporating the Andreotti et al (2018) AHS study results), the arguments advanced by the Zhang et al. (2019) authors in support of the fixed effect model contain methodological and logical flaws.⁹ The correct meta-analysis method here is a random effects analysis (which tends to give wider and more appropriate confidence intervals).

- The Zhang et al. (2019) authors critiqued Andreotti et al. (2018) for using multiple imputation to account for missing data (Andreotti et al. (2018) had a response rate of only about 63% so 37% of the data needed to be imputed) which Zhang et al. (2019) describe as an “exposure simulation” and provide some technical details about why they have concerns about this. Multiple imputation for missing data is a state-of-the-science practice for dealing with missing data; nevertheless, the Zhang et al. (2019) authors correctly point out that Andreotti et al. (2018) should have included the *outcome* information into the process of imputing missing exposure values. Since the missing data of glyphosate exposure of subjects who did not complete the follow-up questionnaire were imputed based on the available information for factors that related to pesticide use such as demographic, medical history, other farm characteristics, and reported pesticide use at enrollment, it would be expected that the impact of failing to include the NHL information would not be substantial. Importantly, Andreotti et al. (2018) conducted a number of sensitivity analyses that suggest the results of the data analysis of imputed data were reasonable and close to that of data analysis which would have resulted using only complete data. For example: for the association between glyphosate exposure and NHL, an estimated risk ratio for quartile 4 ($RR_{\text{Quartile 4}} = 0.90$ (95% CI=0.63 to 1.27) was obtained from the sensitivity analysis using the data of only subjects with complete data vs. an estimated $RR_{\text{Quartile 4}} = 0.87$ (95% CI=0.64 to 1.20) from the analysis where the missing data were imputed.¹⁰ Given these minor differences, TEB believes that the Andreotti et al. (2018) analysis is adequate and represents a sufficiently reliable risk ratio (RR) for incorporation into a meta-analysis.
- Zhang et al (2019) also correctly pointed out another difference between the earlier De Roos et al. (2005) AHS study and the updated Andreotti et al. (2018) AHS study with respect to the reference group selected. Specifically, the De Roos et al. (2005) article selected the lowest quartile as the reference group while the later Andreotti et al. (2018) article selected the unexposed as the reference group. Both studies appeared to show differences between the groups

⁸ Zhang et al. (2019) reported mRR of 1.56 (95% CI: 1.12, 2.16) using a random effects model and the Andreotti et al (2018) data in addition to the fixed mRR estimate of 1.45 (95% CI: 1.11, 1.91) using the earlier AHS study (DeRoos, 2005) study in place of Andreotti (2019).

⁹ See, e.g., various sections in Borenstein, Michael. *Common Mistakes in Meta-analysis and How to Avoid Them*. (Biostat, Inc: Englewood, NJ) 2019. e.g., §8.5 p. 59-63) and Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. *Introduction to Meta-Analysis* (John Wiley and Sons: London) 2008. See also Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. 2010. A basic introduction to fixed effect and random effects models for meta-analysis. *Res. Syn. Meth.* 1:97-111.

¹⁰ $RR_{\text{Quartile 4}} = 0.90$ (95% CI: 0.63,1.27) is listed on page 4 of the publication. $RR_{\text{Quartile 4}} = 0.87$ (95% CI: 0.64, 1.20) is listed in Table 2 of the publication.

that used glyphosate and those that did not¹¹ which could mean that the potential exists for residual confounding¹². It is not clear why Andreotti et al. (2018) did not use the lowest exposed quartile as the reference group, at least as part of a sensitivity analysis, and this appears to be a legitimate critique by Zhang et al (2019). Nevertheless, the (statistically significant) baseline differences between the exposed and unexposed do not appear to be substantive and, in any case, were adjusted for in the Poisson regressions that were performed by both (originally) De Roos et al. (2005) and (subsequently) by Andreotti et al. (2018).

The authors stated that their analyses differ from several earlier meta-analyses by focusing on an *a priori* hypothesis targeting biologically-relevant exposure magnitude and including newly updated AHS information from Andreotti et al (2018). More specifically, the Zhang et al (2019) authors elected with their *a priori* hypothesis to focus on the effect sizes which were associated with and characteristic of high-end exposures to GBHs (where “high” was defined as of greater intensity/magnitude, of longer duration, or of some cumulative combination of the two). For at least Andreotti et al. (2018) -- the largest study and of the highest quality -- this hypothesis does not appear to be supported by initial examination of categorized exposures since there are not statistically significant results, no trend is observed (nor monotonicity), and the confidence interval (CI) around each effect size estimate by categorized exposure overlap considerably. In other words, there is no readily apparent indication of a trend toward higher odds ratios with higher exposures in Andreotti et al (2018) so there appears to be little evidence supporting the authors’ stated *a priori* hypothesis. The table below is an excerpt from Andreotti et al. (2018) and it was the RR and its associated 95% CI of 1.12 (95% CI: 0.83, 1.51) from quartile 4 (Q4) and the 20-year lag that was used by the Zhang et al. (2019) authors as part of their meta-analysis (because this reflects the category with the highest exposure/longest lag (Q4, 20-y lag) and thus most likely to display the largest RR if there was indeed an association).

¹¹ Specifically, De Roos et al. (2005) state that “We compared certain baseline characteristics among the three types of pesticide applicators... [and]... the purpose of the comparison was to identify potential confounders of the glyphosate exposure-disease associations for the various analyses we conducted. Differences between the exposure groups were tested using the chi-square statistics and associated p-values.” They continue, indicating that “significant differences (p<0.05) existed between never exposed and lowest exposed subjects for all of the [baseline] characteristics in Table 1. Lowest- and higher- exposures subjects (p<0.05) also differed on several factors, the most notable being that higher -exposed subjects were more likely to be commercial applicators, to have consumed greater amounts of alcohol in the past year, and to have used other specific pesticides. However, lowest- and higher-exposed subjects were similar to each other (p>0.05) in characteristics including smoking and family history of cancer in a first degree relative. In addition, lowest and higher- exposed subjects were more similar to each other than to their never-exposed counterparts (by qualitative comparison of percentages only) in factors including NC residence, education beyond high school, and use of other pesticides. Because of relative similarities between lowest- and higher-exposed in factors associated with socioeconomic status and other exposures, we decided to conduct some analyses using lowest-exposed rather than never-exposed applicators as the reference group, in order to avoid residual confounding by unmeasured covariates.”

¹² Specifically, if there are systematic differences in observed variables between farmers/applicators that use glyphosate vs. those that don’t, these can be adjusted for (i.e., accounted or corrected for) in the statistical modeling. Nevertheless, such differences in observed characteristics between users and non-users of glyphosate may be symptomatic of other (unmeasured) systematic /characteristic differences that *aren’t* measured in the study. To the extent that these might affect exposure or disease probabilities, such differences would be ‘hidden’ from the analysis and be unable to be adjusted for by the analysis and potentially lead to incorrect inferences. Hence, if there are differences between unexposed (e.g., non-users) and exposed (e.g., users) individuals, it can be desirable to use the lowest category of exposure (as opposed to the unexposed) as the reference category.

Table 3. Cancer incidence in relation to lagged intensity weighted lifetime days of glyphosate use in the Agricultural Health Study

Cancer sites*	Glyphosate use†	5-y lag			20-y lag		
		No. of cases	RR (95% CI)‡	P _{trend} ‡	No. of cases	RR (95% CI)‡	P _{trend} ‡
Non-Hodgkin lymphoma							
	None	150	1.00 (reference)		354	1.00 (reference)	
	Q1	113	0.92 (0.66 to 1.28)		63	1.22 (0.91 to 1.64)	
	Q2	92	0.79 (0.59 to 1.06)		55	1.15 (0.86 to 1.55)	
	Q3	119	1.03 (0.75 to 1.41)		48	0.98 (0.71 to 1.36)	
	Q4	101	0.87 (0.64 to 1.17)	.76	55	1.12 (0.83 to 1.51)	.62

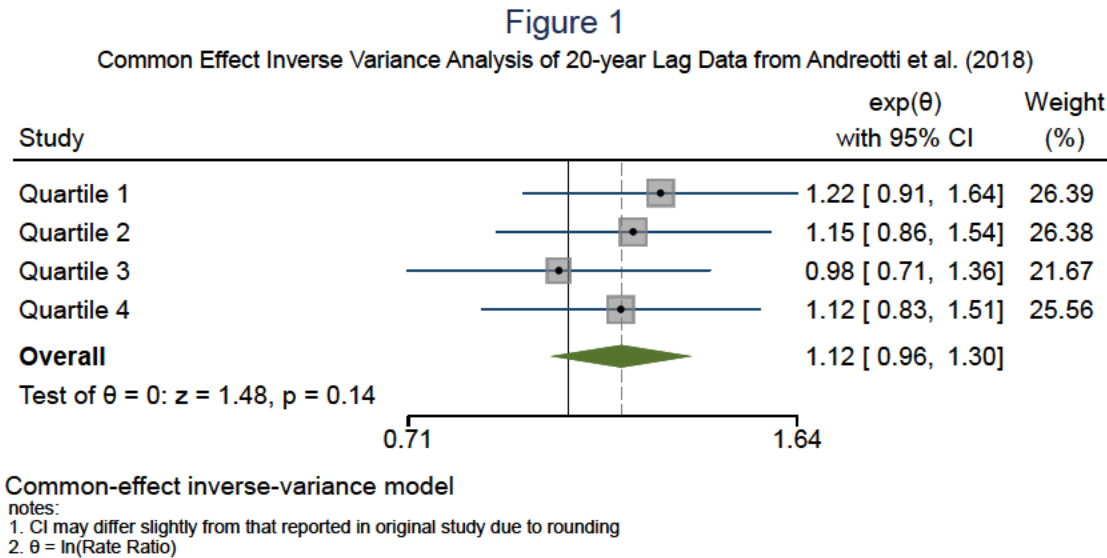
Excerpt copied directly from p. 514 of Andreotti et al (2018)

It seems apparent from the above excerpt, however, that (i) there is no suggestion of a trend toward higher RRs at higher exposures ($p_{\text{trend}}=0.62$), with the Q4 value in fact being only the third highest of the four quartiles value (i.e., one up from the bottom); (ii) none of the RRs associated with any of the quartiles is significant or appear to come close to it; and (iii) all the RRs seem roughly similar at the null $RR \cong 1$. Given that, it doesn't appear that extracting only the Q4 value from the RRs here and choosing to move forward with only that selection is necessarily well-supported or justified, particularly since this considerably lowers the sample size (by about two-fold for this 20 year lag and eight-fold compared to an ever/never analysis). This is of particular importance because Andreotti et al. (2018) is a prospective cohort study that is the highest-quality of all the studies selected for meta-analysis. Thus, it seems there is little justification for any *a priori* hypothesis that there is a dose-response phenomenon with higher doses (exposures) leading to increased risks of NHL here and that there is no clear rationale for Zhang et al. (2019) to choose to use only a small subset of the Andreotti et al (2018) data for their meta-analysis.¹³

¹³ The subset – as indicated in the text- - was the Q4/20 y lag subset which represents the “high end” exposure to GBHs offered Andreotti et al. (2018) and this RR of 1.12 (95% CI: 0.83, 1.51) was used by Zhang et al. (2018) in place of the earlier De Roos et al. (2005) ever-never estimate of 1.10 (95% CI: 0.7, 1.9). Separate high-end estimates were also provided by Eriksson et al (2008) and McDuffie et al. (2001) representing >10 days/yr. (vs. ≤10 days/yr.) and >2 days/yr. vs. (vs. ≤2 days/yr.), respectively; Zhang et al. (2018) similarly used the high end estimates of 2.36 (95% CI: 1.04, 5.37) and 2.12 (95% CI: 1.20, 3.73), respectively, from these two studies in place of those studies' ever/never estimates. TEB notes two things regarding this substitution:

- 1) the Eriksson et al. (2008)-substituted value of 2.36 (95% CI: 1.04, 5.37) from their Table II was based on only 17 cases and 9 controls and was an *unadjusted* effect size because no adjusted effect sizes were provided in the article for the >10 days high end exposure estimate. Table VII in Eriksson et al (2008) suggests that adjustment for age, sex and year of diagnosis/enrolment would bring about a meaningful decrease in the odds ratio for glyphosate had that statistical adjustment been made; this in turn suggests that the > 10 days/yr odds ratio from Ericksson et al (2008) used by Zhang et al. (2018) likely over-estimated any true relationship.
- 2) McDuffie et al. (2001) reports an odds ratio of 1.00 (95% CI: 1.63, 1.57) and 2.12 (95% CI: 1.20,3.73) for >0 to ≤2 days/yr and >2 days/yr., respectively. Zhang et al uses the odd ratio 2.12 (95% CI: 1.20,3.73) representing the high end (>2 days/yr) exposure estimate in place of the 1.20 (95% CI: 0.83, 1.74) odds ratio value associated with the ever/never estimate. Due to recall bias in case-control studies and its tendency to introduce differential misclassification away from the null, this estimate of 2.12 (95% CI: 1.20,3.73) for the odds ratio is likely to overestimate the true relationship. Support for this is provided in McDuffie et al. (2001) Table 5 wherein it can be seen that substantially higher odds ratios are seen for all nine odds ratios in that table associated with higher end days/yr. exposures. For example, there is no reasonable expectation of any relationship between application of sulfur and NHL, yet Table 5 in McDuffie et al. (2001) suggests that applying sulfur ≥ 1 day per year (vs. 0 days per year) more than doubles the risk of NHL (OR=2.12 (95% CI: 1.20, 3.73). Similar increases are seen for 2,4-D, mecoprop, dicamba, malathion, DDT, captan, and carbon tetrachloride. These are all likely reflective of recall bias, or the tendency of cases (here NHL) to mistakenly overestimate exposures and would consequently lead to odds ratios that likely overestimate true effect sizes. Thus, Zhang et al.'s substitution of the McDuffie et al (2001) odds ratio of 2.12 (95% CI: 1.20,3.73) for glyphosate application of >2 d/yr is likely to overestimate any potential true effect.

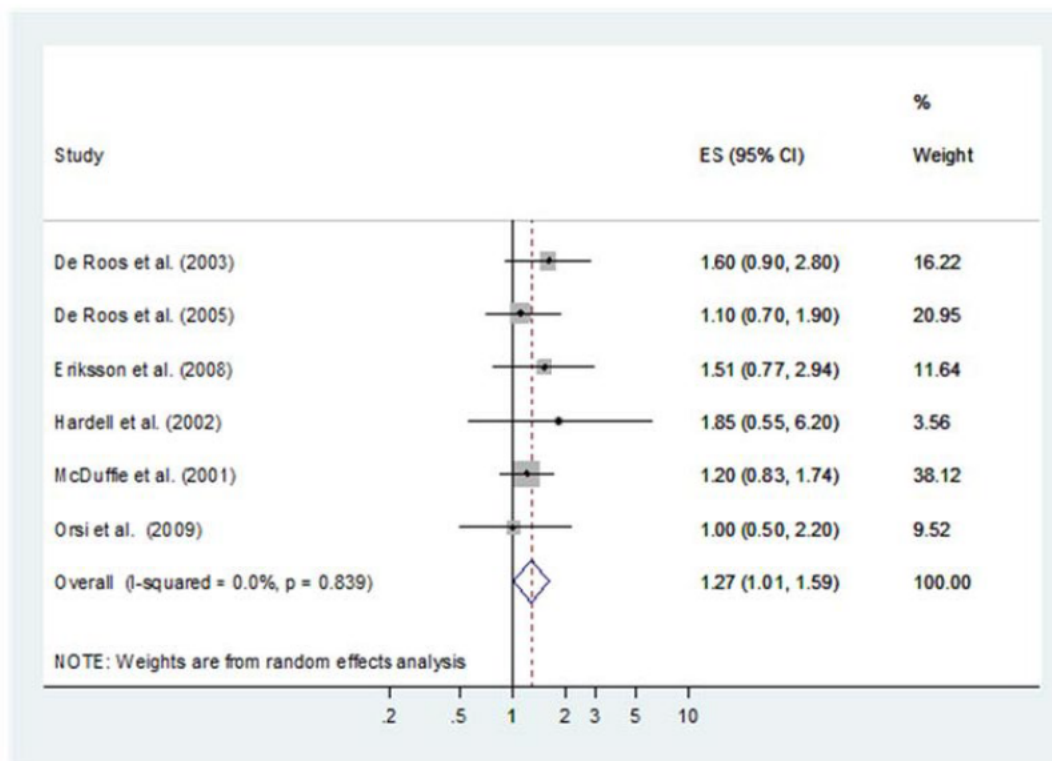
As stated earlier, one of the consequences of this choice is that only a small proportion of the results from the largest, most comprehensive, and best designed study among all those examined gets used (specifically, only the 55 exposed cases in Q4 of the 20 year lag analysis vs. 440 exposed cases in all the quartiles for an ever-use analysis). In fact, there is greater justification for combining Q1-Q4 from the 20-year lag analysis into a single 20 year lagged ever/never category for a meta-analysis. Using a fixed effect (aka “common effect”) inverse variance meta-analysis a RR close to the null value of 1 (RR = 1.12; 95% CI = 0.96, 1.30) would be obtained that is not statistically significant (p-value =0.14), as shown in Figure 1:



(ii) *CEB Update of Revised Estimate:*

The EPA’s December 2017 Revised Glyphosate Issue Paper used single summary measures (i.e., ever/never effect sizes) from the original six NHL studies identified. The results from Andreotti et al. (2018), which was published online at the time, were not incorporated into the EPA analysis at that time. The meta-estimate of 1.27 (95% CI: 1.01, 1.59) based on this analysis was statistically significant, with the lower limit of the 95% CI just slightly over 1. Figure 2 is the forest plot displaying the meta-analysis results excerpted from the December 2017 EPA Revised Glyphosate Issue Paper.

Figure 2. Forest Plot and Meta-analysis for NHL from EPA's December 2017
Revised Glyphosate Issue Paper



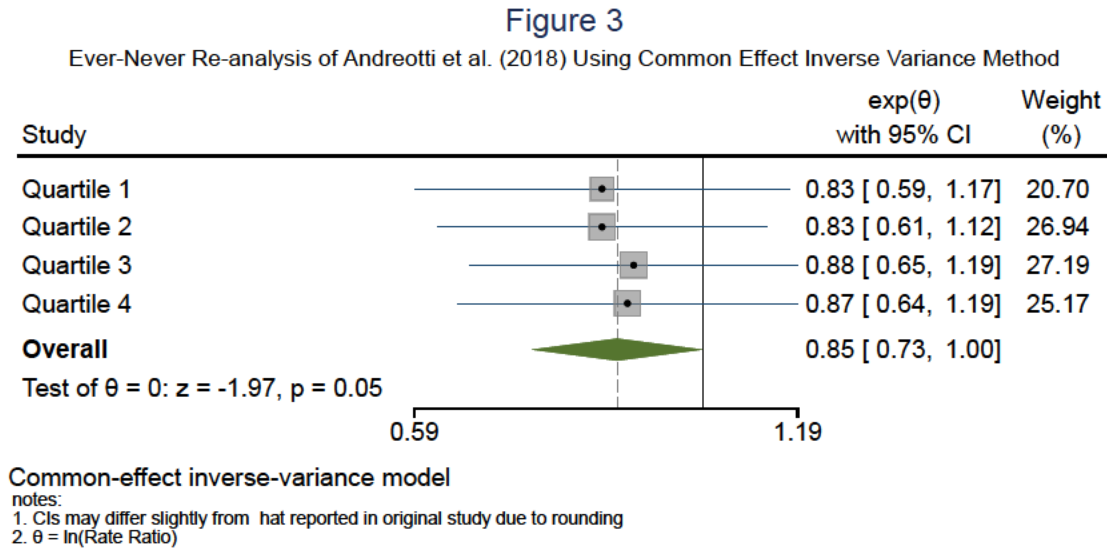
The Andreotti et al. (2018) AHS study updated the De Roos et al (2005) AHS study to include (as indicated above) more recent AHS data: this added 11-12 additional years of follow-up data to De Roos et al (2005) and increased by five-fold the number of NHL cases (n=575 rather than n=92)¹⁴. TEB has been requested to update its previous meta-analysis (illustrated in Figure 2 above from the EPA Revised Glyphosate Issue Paper) by replacing the earlier AHS data from DeRoos et al (2005) with the updated AHS data from Andreotti et al (2018).

Unlike De Roos et al. (2005) and the other five studies included in the previous EPA meta-analysis, Andreotti et al. (2018) provided risk estimates by exposure *quartile* and did **not** report risk estimates on an ever/never basis as did the earlier De Roos et al. (2005) study and other publications.¹⁵ In order to incorporate the Andreotti et al. (2018) data into the meta-analysis, the ever/never risk estimates were

¹⁴ HED prepared an independent review of this AHS study after the 2016 SAP (A. Aldridge, DP Barcode D444727, 12/12/2017). See <https://beta.regulations.gov/document/EPA-HQ-OPP-2009-0361-0074>.

¹⁵ This may be because the Andreotti et al. (2018) exposed counts were larger than the other studies and thus the authors were able to break this out on a quartile basis. NHL counts for Q1 through Q4 in Andreotti et al. (2018) were 102, 93, 106, and 103, respectively.

calculated from the data expressed in exposure quartiles by Andreotti et al (2018). Specifically, this was done using a fixed effect (aka “common effect”) meta-analysis technique which is appropriate when attempting to combine effect size estimates from a *single* study.¹⁶ The resulting estimate for Andreotti et al. (2018) on a comparable ever/never basis is a rate ratio (RR) of 0.85 (95% CI: 0.73, 1.00) as illustrated below in Figure 3.

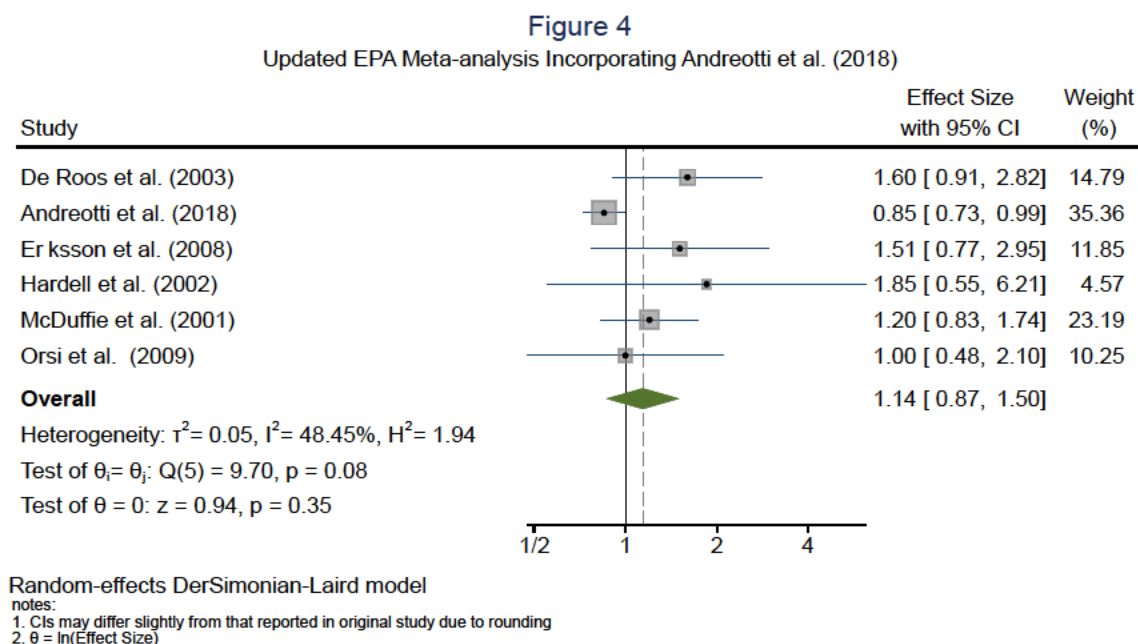


Using this updated risk estimate and substituting out the (earlier) AHS risk estimate from De Roos et al. (2005) of OR = 1.1 (95% CI: 0.7, 1.9) produces the following set of effect sizes for use in a new meta-analysis that incorporates the newest (updated) AHS NHL study results from Andreotti et al (2018).

Study	Risk Estimate (OR or RR)	Lower bound of CI	Upper bound of CI
De Roos et al. (2003)	1.60	0.90	2.80
Andreotti et al. (2018) ^a	0.85	0.73	1.00
Eriksson et al. (2008)	1.51	0.77	2.94
Hardell et al. (2002)	1.85	0.55	6.20
McDuffie et al. (2001)	1.20	0.83	1.74
Orsi et al. (2009)	1.00	0.50	2.20
^a Andreotti et al (2018) substitutes for the earlier De Roos et al. (2005) estimates of 1.1 (95% CI: 0.7, 1.9)			

¹⁶ For this type of analysis, a fixed effect model is appropriate. See, e.g., various sections in Borenstein, Michael. *Common Mistakes in Meta-analysis and How to Avoid Them*. (Biostat, Inc: Englewood, NJ) 2019 and Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. *Introduction to Meta-Analysis* (John Wiley and Sons: London) 2008.

Using these data to update the meta-analysis that was originally performed for the December 2017 EPA Revised Glyphosate Issue Paper produces the following forest plot in Figure 4 with a meta-estimate of the effect size of 1.14 (95% CI: 0.87, 1.50).

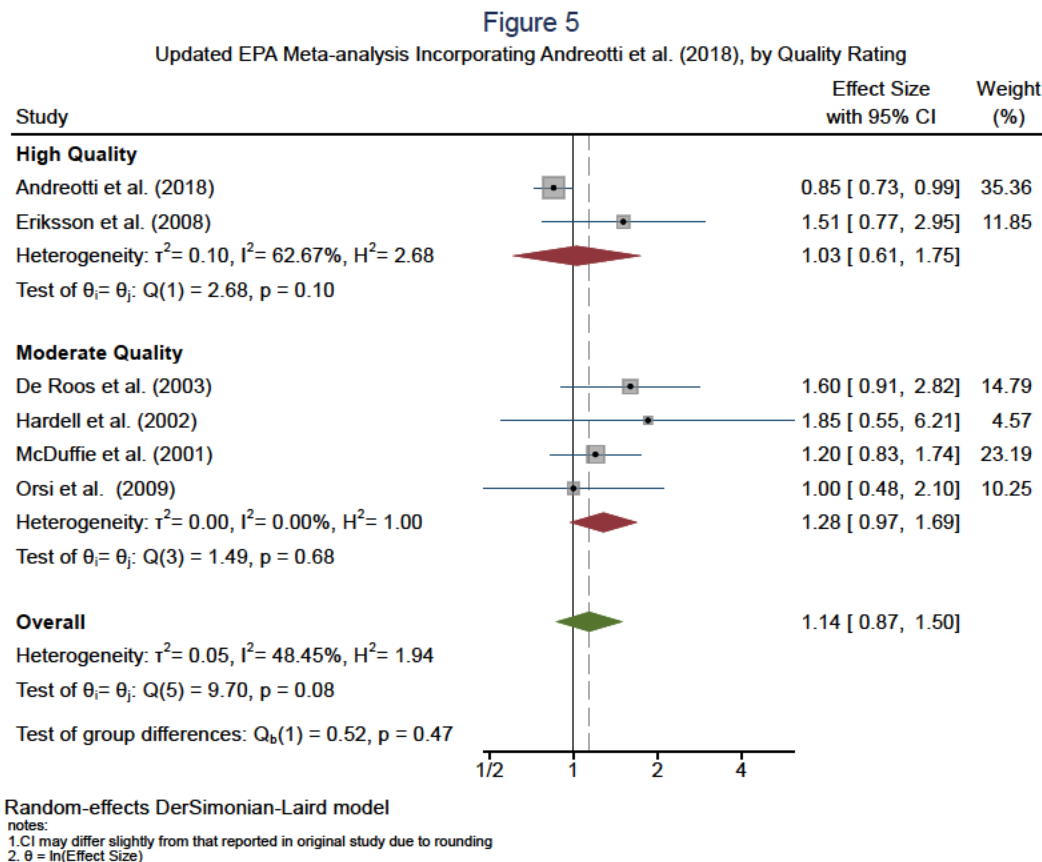


As expected, the larger sample size and tighter 95% CI from Andreotti et al. (2018) increased the weight of the AHS cohort study to 35.36% (from 20.95% when using the smaller De Roos et al. (2005) study). The authors of the Zhang et al (2019) review article did not perform this ever-never meta-analysis presumably because Andreotti et al. (2018) reported estimates by quartile and did not provide the ever/never estimates present in and comparable to the original six studies. This updated meta-estimate of 1.14 (95% CI: 0.87, 1.50) compares to EPA's earlier (December 2017) estimate of 1.27 (95% CI: 1.01, 1.59) when the AHS data from De Roos (2005) was included. Therefore, incorporation of the study results from Andreotti et al (2018) yielded a smaller effect size, which is no longer statistically significant.

Finally, there has been some interest in the past in performing these analyses after separating the high and moderate quality studies and seeing how they compare. Per the Revised Glyphosate Issue Paper, the following quality ratings were assigned:

Study	Quality Ranking
De Roos et al. (2003)	Moderate
De Roos et al. (2005)	High
Eriksson et al. (2008)	High
Hardell et al. (2002)	Moderate
McDuffie et al. (2001)	Moderate
Orsi et al. (2009)	Moderate

These are the same ratings assigned (independently) by the Zhang et al. (2019) study authors. Substituting the newer (and similarly high ranked) Andreotti et al. (2018) study for the earlier De Roos et al. (2005) high-ranked AHS study produces the following forest plot/meta-analysis (Figure 5):



As can be seen, the two high-ranked studies also produce a non-statistically significant meta-estimate of 1.03 (95% CI: 0.61, 1.75) and the four moderately ranked studies produce a similarly non-significant meta-estimate of 1.28 (95% CI: 0.97, 1.69) for the effect size. As expected, the overall meta-estimate of 1.14 in Figure 5 and its confidence interval are the same as shown earlier in Figure 4.

Summary and Conclusions for Zhang et al. (2019):

Overall, HED does not believe Zhang et al. (2019) used appropriate methods to perform their meta-analyses. The supplemental analyses presented here indicates that lower and non-statistically significant meta-estimates would be obtained if the Andreotti et al. (2018) study is more properly incorporated into the meta-analysis done previously and appearing in the EPA 2017 Revised Glyphosate Issue. Specifically, the Andreotti (2018)-updated meta-estimate is 1.14 (95% CI: 0.87, 1.50) and is no longer statistically significant. This meta-analysis represents an update to the one appearing in the December 2017 EPA Revised Glyphosate Issue Paper in which a statistically significant meta-estimate of the effect size of 1.27 (95% CI: 1.01, 1.59) was reported. As expected in the updated random effect meta-analysis presented here, the larger sample size and tighter confidence interval in Andreotti (2018) means that the

weight of this AHS study increases to 35.36% (from 20.95% when the earlier – and smaller - DeRoos (2005) AHS study was used in a similar random effects analysis). The Zhang et al. (2019) authors did not perform this analysis because Andreotti et al. (2018) did not include an ever/never estimate in their AHS update but instead provided estimates by quartile (and also by lagged quartile). The analysis presented here by EPA in the memorandum used a fixed effect (aka “common effect”) inverse variance model to combine the Andreotti-generated quartile-based estimates and create an ever-never estimate.

The Zhang et al. (2019) authors conducted their own literature search and used the same six studies that EPA used in its evaluation. Two studies were from the U.S., one was from Canada, two studies were from Sweden, and one study was from France. One of these was a prospective cohort study, with the remainder being case-control. Quality scorings of these studies were performed by Zhang et al. (2019) based on the Newcastle-Ottawa Scale (NOS) with the two highest scoring studies (7 or 8 points) being Andreotti et al. (2018)/DeRoos (2005), the prospective AHS studies, and Ericksson, a case control study. The remaining studies scored either 6 points or 2 points by the NOS, with this latter low score applying only to Orsi et al. (2009). These ratings match the rankings given by EPA in its 2017 Revised Glyphosate Report which ranked DeRoos et al. (2005) and Ericksson et al. (2008) as high and the remainder moderate.

Further regarding the Zhang et al. (2019) publication, the authors state that this study differs from several earlier meta-analyses by focusing on an *a priori* hypothesis targeting biologically-relevant exposure magnitude (using only the risk estimate of the highest exposure and the longest duration of exposure group) and including newly updated AHS information from Andreotti et al (2018). This hypothesis does not appear to be well supported by initial looks at the Andreotti et al. (2018)-categorized 20 year lag rate ratio estimates since there are no statistically significant results, no trend in rate ratios (nor monotonicity), and the confidence intervals around each categorized exposure overlap considerably and cover the null value of 1 for all exposure quartiles. In addition, the authors focused on the results from a fixed effect meta-analysis performed on the effect sizes estimated for highest exposure categories. The use of a fixed effect meta-analyses (instead of random effects) for this kind of data is incorrect. The authors did, nevertheless, perform a random effects analysis and present these results but indicated that they did not emphasize them.

In summary, the *a priori* hypothesis that higher/longer exposures produce larger effect sizes advanced by Zhang et al. (2019) in their analysis does not appear to be supported by the new AHS data from Andreotti et al. (2018) which is the largest, best-designed high quality study examined. EPA has used this Andreotti et al. (2018) AHS data to update its December 2017 meta-analysis by replacing the De Roos et al. (2005) AHS results and revised/updated our meta-estimate to a non-statistically significant 1.14 (95% CI: 0.87, 1.50). This revised estimate incorporates the most recent AHS data from Andreotti et al. (2018) and does not impact the conclusions presented in the EPA Revised Glyphosate Issue Paper which concludes that the strongest support based on the weight-of-evidence is for glyphosate being categorized as “not likely to be carcinogenic to humans”.

PART II. EPA Review of Leon et al. (2019)

Leon et al. (2019) published a summary review/meta-analysis investigating pesticide use and the risk of NHL in cohorts from France (Agriculture and Cancer, **AGRICAN**), Norway (Cancer in the Norwegian Agricultural Population, **CNAP**) and the USA (**AHS**) as part of the international AGRICOH consortium (see <https://agricoh.iarc.fr>). The Leon et al. authors used data from these three large cohort studies to explore the relationship between the use of selected pesticide chemical groups as well as various individual pesticide chemicals -- including glyphosate -- and the risk of NHL overall and four major NHL subtypes; this was done in a combined population of nearly 320,000 farmers and farmworkers totaling

3.5 million person-years of exposure. The four major NHL subtypes investigated were: (i) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); (ii) diffuse large B-cell lymphoma (DLBC); (iii) follicular lymphoma (FL); and (iv) multiple myeloma/plasma-cell leukemia (MM). More specifically, the **French AGRICAN study** component enrolled 181,747 men in 2005-2007 who met various inclusion criteria including being (i) ≥ 18 y.o.; (ii) affiliated with the national health insurance system of agricultural workers; and (iii) residing in 2005 in one of 11 departments in France covered by population-based cancer registries. The cohort investigated here consisted of active and retired farm owners and farm workers. Members were enrolled after returning self-administered questionnaires that covered historical use information on 13 crops and 5 animal species (first and last year of production) and performance of pesticide treatment tasks (first and last year performed, per crop or animal species). For this study, AGRICAN cohort members were linked with cancer and mortality registries and the French National Death Index through December 2009. The **Norwegian CNAP study** considered owners and non-owners using a farm ("farm holders") and their families that were included in at least one of five national agricultural and horticultural censuses performed during 1969, 1974, 1979, 1985, and 1989 by Statistics Norway (n=147,134). The **US AHS study** has been described previously; briefly, it consisted of 52,394 private pesticide applicators (farmers) and 4916 commercial pesticide applicators registered to apply restricted use pesticides in Iowa and North Carolina. Members of the AHS cohort were enrolled during 1993-97 and completed questionnaires on agricultural practices, crops, and livestock and the use of more than 50 individual pesticide active ingredients, including glyphosate. Applicators completed a second questionnaire approximately five years later that provided details on pesticide use since enrollment. Cohort members have been routinely and regularly linked to the Iowa and North Carolina cancer and mortality registries and the National Death Index through 31 December 2011 for Iowa participants and 31 December 2010 for North Carolina participants. The summary review/meta-analysis performed here by the Leon et al. (2019) study authors considered only farmers (and not commercial applicators) from the US AHS. After additional adjustments¹⁷, a total of n= 127,282, 137,821, and 51,167 individuals were available for use from the AGRICAN, CNAP, and AHS studies, respectively. Combined, this represents 316,270 individuals and 3,574,815 person-years of follow-up from January 1993 through December 2011, with a median follow-up period of 16 years. During this follow-up a total of 2545 first incident NHL cases were observed (to include both Hodgkins lymphoma and NHL) of which 95.4% were NHL with a median age at diagnosis of 69 years. AGRICAN, CNAP, and AHS contributed 18.1%, 61.6%, and 20.3% of cases to this analysis, respectively.

Study population demographic and other characteristics differed by cohort: for example, AHS cohort members at the start of follow-up were younger than those in CNAP and AGRICAN (median age of 46 years in AHS vs. 51 and 67 years for CNAP and AGRICAN respectively). Half of the AGRICAN cohort consisted of retired farm owners or workers and 44% were female compared with 16% in CNAP and 3% in AHS. Nearly all AHS cohort members (99%) used pesticides (in general, not specifically glyphosate) while only 68% and 63%, respectively did in AGRICAN and CNAP, and of the combined cohort, 63% were classified as ever having been exposed to at least one of the investigated pesticides. Glyphosate in particular was classified as used by 36%, 38%, and 83% of the farmers or farmworkers in the AGRICAN, CNAP, and AHS study cohort populations, respectively.

For the AGRICAN and CNAP studies, data were crossed with country-specific crop-exposure matrices (CEMs) to estimate ever-use of glyphosate and represent *potential* use while for AHS cohort members, self-reported ever-application was used to assess exposure. For AGRICAN, the French PESTIMAT matrix was used to obtain historical use information which incorporated information on the first and last year in which glyphosate was authorized and recommended for use in France on a given crop; potential

¹⁷ Additional adjustments included accounting for emigration or loss to follow-up, prevalent cancer at the start of cancer follow-up, or for being nonfarmers (for AGRICAN), dying before the start of cancer follow-up (for CNAP), and being commercial applicators (for AHS).

exposure in the French AGRICAN was assumed if an individual cultivated a given crop, marked the study questionnaire as having treated the crop with (any) pesticide, and glyphosate was authorized and recommended for use in a given year. In CNAP, matrices were constructed considering in part the first and last year in Norway that glyphosate was authorized for use on each of the selected crops. The French and Norwegian CEMs extended from 1950 until the last year of cancer follow-up. Potential exposure to glyphosate in the Norwegian CNAP was assumed if a farm holder reported cultivating a given crop, owned spraying equipment or spent money on pesticides, and glyphosate was sold in Norway and registered for use on the crop in a given year. As stated before, the AHS cohort members self-reported use of glyphosate and thus no CEM or assumptions regarding potential exposure were needed.

Cox proportional hazards (PH) analysis was done separately for each of the three study cohorts and used to estimate both fully-adjusted and minimally-adjusted hazard ratios (HRs) and their 95% CIs for incident NHL for ever-use of glyphosate assuming time-independence of covariates. The endpoint was the first incident NHL during follow-up, with follow-up beginning on 01 January 1993 corresponding to the date of enrollment for AGRICAN and AHS and (also) 01 January 1993 for CNAP, the earliest year of follow up in the AHS. Follow-up time for the PH assessment was calculated from the start of follow up to the first date of any of the following: (i) first incident cancer (except non-melanoma skin cancer); loss to follow-up or migration out of the cancer registry area; (iii) death; or (v) end of follow-up. Multiple imputation was used for missing data in AGRICAN and AHS for crop, pesticide treatment task, period of production and period of pesticide treatment task for the former survey and for pesticides applied for the latter; no imputation was required for CNAP since exposure data were derived from compulsory agricultural censuses and the information from farm-holders was thus complete. The reference category for the PH analysis consisted of individuals classified as never exposed to glyphosate. All models initially used age at the date of censoring as the time scale and were adjusted for sex and animal production. For AGRICAN, additional covariates included retirement status while for AHS this included state of residence (either Iowa or North Carolina). Subsequently, fully adjusted models were separately constructed for each study cohort. For AGRICAN, adjustment for the number of crops personally treated with pesticides was added as an ordinal variable to approximate increasing opportunity for pesticide exposure. For CNAP, adjustment for pesticide was used instead since similar information was not available. For CNAP and AHS, adjustment was made using a cohort-specific set of active ingredients.

PH models were run first individually for each cohort, with the resulting estimates combined using random effects meta-analysis based on the adjusted results from the three international cohorts. The authors reported no observed association between ever use of glyphosate and NHL (HR=0.95 (95% CI: 0.77,1.18), n=1131 exposed cases) with some evidence of heterogeneity among cohorts ($I^2=57\%$, $p_{\text{heterog}}=0.10$).

The authors also investigated four NHL subtypes associated with glyphosate and only one – DLBCL at a mHR of 1.36 –was elevated (although not significantly (95% CI: 1.00, 1.85), with n=221). as follows:

- Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL): HR=0.92 (95% CI: 0.69, 1.24), n= 252;
- Diffuse large β -cell lymphoma (DLBCL): HR=1.36 (95% CI: 1.00, 1.85), n= 221^{18,19};

¹⁸ The Leon et al (2019) authors state that there was no evidence of heterogeneity among the three cohorts for DLBCL, that cohort-specific CIs were wide, and only the CNAP cohort --accounting for 45% of exposed cases -- excluded the null value. Adjusting the CNAP value for ever use of other pesticides (linuron, aldicarb, mancozeb, DDT, lindane, and deltamethrin), the authors state, generated a fully-adjusted HR of ever-use of glyphosate of 1.67 (95% CI: 1.05, 2.65), higher than the minimally adjusted estimate of 1.26 (95% CI: 0.97-1.65) which was driven primarily by adjustment for animal production and DDT use.

¹⁹ For DLBCL, Andreotti et al. (2018) reported ever-never RRs by quartile ranging from 0.94 to 1.13 (n=22-30), and none being statistically significant and a p-for- trend-value of 0.83. The ever-never HR value reported here by Leon et al. (2019) for DLBCL

- Follicular lymphoma (FL): HR=0.79 (95% CI: 0.52, 1.21), n= 105; and
- Multiple Myeloma/plasma-cell leukemia (MM): HR=0.87 (95% CI: 0.66, 1.15), n=240.

Considered individually, only the Norwegian CNAP study excluded the null value for the DLBCL NHL subtype with HR=1.67 (95% CI: 1.05, 2.65) based on 100 cases, with the AHS showing a HR for DLBCL of 1.2 (95% CI: 0.72, 1.98) based on 93 exposed cases and the AGRICAN study showing a HR of 1.06 (95% CI: 0.51, 2.19) with 28 cases.

Summary and Conclusions for Leon et al. (2019):

The Leon et al. (2019) review article used data from three international cohorts – the French AGRICAN study, the Norwegian CNAP study and the US AHS study -- to investigate the putative relationship between a number of pesticides, including glyphosate, and NHL; this was performed for both NHL overall (total) and by NHL broken down into four major subtypes. The study harmonized available exposure data from the three independent agricultural cohorts, thereby increasing the numbers of NHL cases (and exposed cases, particularly) which increases the ability of the combined study to detect associations. In sum, the study cumulated more than 300,000 farmers/farmworkers from France, Norway, and the US which represent more than 3.5 million person-years of exposure follow-up time from 1993 through 2011 with a median follow-up time of 16 years. For glyphosate, no significantly increased risks of NHL overall or of three subtypes were observed; for the DLBCL subtype, a somewhat elevated but non-significant relationship was seen (HR=1.36 (95%CI: 1.00, 1.85; n=221 exposed cases). The corresponding HR for the Leon et al. (2019) analysis of AHS for this NHL subtype is smaller, at HR=1.2 (95% CI: 0.72, 1.98) based on 93 exposed cases and for the AGRICAN study smaller still (HR = 1.06 (95% CI: 0.51, 2.19) with 28 cases).

The Leon et al. (2019) review has a number of strengths. It brings together and combines three very large international prospective cohort studies which increases its ability to detect epidemiological associations. There are, however, also a number of limitations. For example, only one of the two cohorts, the AHS cohort, uses actual exposure information collected by individuals through self-administered questionnaires; the French AGRICAN study and the Norwegian CNAP study instead rely on information from CEMs to derive estimates of ever-exposure to glyphosate (among other pesticides). No actual pesticide exposure measurements were made in the AGRICAN or CNAP studies nor were specific questions about specific pesticide applications or application practices asked; instead, a variety of very general and very generic assumptions were made which likely lead to what might be a substantial degree of exposure misclassification. In addition, the study protocol was such that exposure misclassifications may have been exacerbated since analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred and which may equal or exceed pesticide exposure through application. An additional complication was that such re-entry work was not evenly distributed through the cohort. For example, 73% of the males and 56% of the females in AGRICAN reported performing re-entry work in vineyards which is a rarely reported crop in the US AHS

is 1.36 (95% CI: 1.00, 1.85). Cohort specific HRs for ever use of glyphosate and DLBCL are as follows: AGRICAN: 1.06 (95% CI: 0.51, 2.19) with n=28 exposed cases; CNAP: 1.67 (95% CI 1.05, 2.65) with n=100 exposed cases; and AHS: 1.20 (95% CI: 0.72, 1.98) with n=93 exposed cases. Leon et al. (2019) reported a number of exposed cases that is lower than that reported by Andreotti (2018) for the AHS study (see p. 513, Table 2 in Andreotti); some reasons for this difference (as reported by the Leon et al. authors) include the fact that the AHS study included 4619 commercial applicators that were excluded from the Leon et al (2019) analysis and excluded 1620 private users with information on ever use of glyphosate but did not report frequency of use. In addition, the follow up time was longer in the Andreotti et al. (2018) publication (through 2012 and 2013) and thus contained more DLBCL cases (130 vs. 113 cases). Finally, the statistical adjustments that were made were different between the US AHS study and the AGRICAN study examined here: The AGRICAN study did not adjust for cigarette smoking, alcohol intake, or family history of cancer but *did* adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study.

(1%) -- and consisted itself of 97% male farmers. In addition, the cohorts also differed in fundamental ways. For example, AHS cohort members were younger at start of follow-up (median age = 46 years) as compared to those in CNAP (median =51 years) or AGRICAN (median=67 years) with in fact about half of the AGRICAN cohort consisting of retired farm owners and farm workers. Further, 44% of AGRICAN participants were female compared to only 16% in CNAP and 3% in AHS. In the AHS, 99% of participants used pesticides (in general); in AGRICAN and CNAP, the percentages were respectively only 68% and 63%. Further, different statistical adjustments were made depending on what covariates were measured in each of the individual cohorts: The AGRICAN study did not adjust for cigarette smoking, alcohol intake, or family history of cancer as the US AHS did, but did adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study. The Leon et al (2019) authors do state that improvements are planned, specifically indicating that the specificity of the exposure assignments will be improved by incorporating the probability of pesticide use and adding parameters reflecting duration, frequency, and use intensity.

In sum, AGRICOH combined three cohorts – one from France (AGRICAN), one from Norway (CNAP) and one from the US (AHS) and did not find a statistically significant relationship between ever-exposure to glyphosate and NHL overall (HR=0.95 (95% CI: 0.77,1.18), n=1131 exposed cases). A somewhat elevated HR was found for one NHL subtype (DLBCL) at a mHR of 1.36, but the 95% confidence interval for this included 1.0. While the AGRICOH analysis benefited from a combined cohort of more than 300,000 farmers and farmworkers from France, Norway, and the USA representing more than 3.5 million person-years of exposure, only one of the three international cohorts used actual measurement instruments (self-administered questionnaire) for glyphosate exposure. Too, the nature and characteristics of the three cohorts differed in substantive ways and is not clear that the statistical adjustment made were necessarily adequate to account for these differences. We conclude that this additional information provided in Leon et al (2019) combining the AGRICAN, CNAP and AHS studies does not impact the conclusions presented in the EPA Revised Glyphosate Issue Paper which itself concludes that the strongest support based on the weight-of-evidence is for glyphosate being categorized as “not likely to be carcinogenic to humans”.

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Exhibit 12



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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

April 18, 2019

MEMORANDUM

SUBJECT: Glyphosate: Response to Comments, Usage, and Benefits (PC Codes: 103601
103604, 103605, 103607, 103608, 103613, 417300)

FROM: Caleb Hawkins, Biologist *Caleb Hawkins*
Biological Analysis Branch

Charmaine Hanson, Economist *Charmaine Hanson*
Dexter Sells, Economist *Dexter Sells*
Economic Analysis Branch

THRU: Monisha Kaul, Chief *Monisha Kaul*
Biological Analysis Branch
Biological and Economic Analysis Division (7503P)

Tim Kiely, Chief *Tim Kiely*
Economic Analysis Branch
Biological and Economic Analysis Division (7503P)

TO: Khue Nguyen, Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division (7508P)

BEAD Product Review Panel Date: November 14, 2018

SUMMARY

Glyphosate is the most commonly used herbicide in the United States, in terms of area treated. It is a broad-spectrum herbicide that controls broadleaf, sedge, and grass weeds with minimal residual toxicity to crops or non-target vegetation. Glyphosate is registered for use in agriculture, including horticulture, viticulture, and silviculture, as well as non-agricultural sites including commercial, industrial, and residential areas. On average, eighty-four percent of glyphosate applied in agricultural settings, in terms of pounds, is applied to soybeans, corn, or cotton per year. These three field crops all have glyphosate-resistant varieties that have been widely adopted and glyphosate is used on a large majority of acres of these crops.

About 280 million pounds of glyphosate are applied to an average of 298 million acres of crop land annually. In addition to providing broad-spectrum control, it is also relatively inexpensive, averaging between \$1 and \$13 per acre across agricultural use sites. Many high value crops (e.g., tree nuts, grapes, vegetables) and large acreage field crops (e.g., soybean, cotton, corn) have a large percentage of acres treated with glyphosate, implying a large majority of growers find it useful. Glyphosate provides good margins of crop safety, particularly for crops that have been engineered to be resistant to over-the-top applications of glyphosate at late-postemergence. Across many use sites, it is simple to use (i.e., it has broad-spectrum of control, minimal reentry intervals and minimum pre-harvest intervals).

In addition to agricultural uses, glyphosate is important for noxious and invasive weed control in aquatic systems, pastures/rangelands, public lands, forestry, and rights-of-way applications. Glyphosate is the leading herbicide used to control invasive species in the United States. Glyphosate is important for rights-of-way sites because it helps protect the stability of the surface and provides an unobstructed view from undesirable vegetation. Rights-of-way applications are critical to maintaining vital infrastructure and safety for transportation, distribution of goods and services (railways and roadways) and utilities (electric and gas). Glyphosate is an effective herbicide for rights-of-way because of its low cost and broad-spectrum. Glyphosate applications help to keep water resources open for navigation and help maintain water quality, habitat restoration, and recreation.

Glyphosate is also in numerous residential products and provides broad-spectrum weed control to users that include homeowners and landscaping operations. Millions of pounds of glyphosate are applied to non-crop sites every year.

To address potential risks to non-target organisms in areas adjacent to treated areas, the Agency is considering use restrictions for spray drift management. Proposed mitigation includes restrictions on applications during temperature inversions and specification of droplet size, boom length, and spray release height. The Agency is considering increasing the allowable wind speed for aerial applications in conjunction with shorter boom length.

Restrictions due to possible temperature inversions may impact the usability of glyphosate products; however, most spray drift management measures are not expected to substantially reduce the benefit of glyphosate to users.

While resistance has been widely reported and confirmed in 17 different weed species in the United States (Heap, 2018), glyphosate remains a useful herbicide for users in agricultural and non-agricultural settings because it has a broad spectrum, is simple to use, and is often cost-effective. However, the benefit of glyphosate to users is contingent upon its effectiveness. If glyphosate-resistant biotypes are present in a field or treatment area, then the benefits of glyphosate could be reduced for those users.

BACKGROUND

FIFRA Section 3(g) mandates that the Environmental Protection Agency (EPA or the Agency) periodically review the registration of all pesticides to ensure that they do not pose unreasonable adverse effects to human health and the environment. This periodic review is necessary in light of scientific advancements, changes in policy, and changes in use patterns that may alter the conditions underpinning previous registration decisions. In determining whether effects are unreasonable, FIFRA requires that the Environmental Protection Agency consider the risks and benefits of any use of the pesticide.

The Office of Pesticide Programs (OPP) completed risk assessments for glyphosate and found potential risks to birds, mammals, and terrestrial/aquatic plants.

The Agency is considering spray drift management measures to reduce the potential for exposure to non-target organisms. Spray drift management measures include:

- Applicators must not spray during temperature inversions.
- For aerial applications, do not apply when wind speeds exceed 15 mph at the application site. If the wind speed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor blade diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.
- For aerial applications, the release height must be no higher than 10 feet from the top of the crop canopy or ground, unless a greater application height is required for pilot safety.
- For ground boom applications, apply with the release height no more than 4 feet above the ground or crop canopy.
- For ground and aerial applications, select a nozzle and pressure that deliver fine or coarser droplets as indicated in nozzle manufacturers' catalogues and in accordance with American Society of Agricultural & Biological Engineers Standard 572.1 (ASABE S572.1).

This memo describes the benefits of glyphosate in agricultural and non-agricultural use sites and discusses EPA's proposed mitigation measures and their possible impacts on users. The information in this assessment may be used during the risk mitigation process and development of the Proposed Interim Decision (PID) for glyphosate. This memo also summarizes public comments received by EPA after the draft human health and ecological risk assessments were published.

METHODOLOGY

The benefits of the use of a pesticide are typically measured in comparison to the next best available pest control option in terms of improved outcomes, such as yield or quality, or in decreased pest control costs, where costs are considered broadly to include not just monetary costs but also factors such as managerial effort and complexity. Given the wide range of use sites for which glyphosate is registered and the low risks of concern, this assessment is qualitative in nature. Rather than focus on specific crops and target weeds, this assessment identifies benefits to glyphosate users for several broad groups of crops and use sites.

BEAD considered the following sources of information to analyze glyphosate's benefits:

- Pesticide market research data (MRD) which provides pesticide usage information, including application rates, number of applications, and percentage of the crop treated for about 60 surveyed crops.
- Kline and Company market research data which provide pesticide usage information for many non-agricultural uses, including the residential consumer market, as well as pasture and rangeland.
- Florida Fish and Wildlife Conservation Commission which provides information on the aquatic use of glyphosate.
- U.S. Forest Service (USFS) data which provides information on invasive weed control.
- Comments from stakeholders following publication of the glyphosate draft human health and ecological risk assessments.
- Extension literature.
- Papers from the open scientific literature.

BEAD analysts first consulted agricultural pesticide usage data to identify important uses that may be associated with potential risks (i.e., those accounting for the most acres treated and/or amount of glyphosate used). These sites are arranged by groups which have similar production and weed control practices. The groups are:

- Field crops, including:
 - Genetically modified glyphosate-resistant (GR) field crops (corn, soybeans, cotton, canola, sugar beets, and alfalfa)
 - Non-glyphosate-resistant varieties of these crops and other field crops (e.g., wheat, dry beans and peas, peanuts, sunflowers)
- Orchards and vineyards (e.g., fruit and nut trees, citrus, grapes)
- Vegetables and other crops (e.g., melons, berries, fruiting vegetables, onions, asparagus)
- Pasture and rangeland
- Non-agricultural uses (e.g., rights of way, turf, aquatic sites, etc.)

For each use group, information from the relevant sources listed was used to develop a qualitative assessment of the role of glyphosate in weed management and identify the advantages glyphosate provides the user.

The next section summarizes relevant comments received, most of which describe various benefits of glyphosate. These comments provide a basis for further discussion in the subsequent sections of this document.

PUBLIC COMMENTS

Thousands of comments were received from various individuals, growers, businesses, commodity groups and other stakeholders. Comment summaries and BEAD's responses to benefits and use comments are grouped according to general benefits (that apply to nearly all glyphosate uses) and according to the broad categories of glyphosate's uses: field crops (genetically-engineered to be glyphosate-resistant [GR] and non-GR field crops), other agricultural uses, i.e., vegetables and tree crops and vines, non-agricultural uses (forestry, rights-of-way, etc.) and residential/homeowner uses.

The substantive comments of relevance to this assessment and addressed subsequently in this memo are denoted below by use of the four-digit number that was assigned to the individual submission. For instance, the comment EPA-HQ-OPP-2009-0361-1001 is identified by the last four digits (-1001) and is associated with an individual comment submission. All received comments can be found in the docket.

Commenters by Affiliation:

- a) Academic/Extension: Weed Science Society of America (-2185), LSU Ag Center (-1655).
- b) Commodity Groups/ Trade Organizations:
 - i. General Organizations: Agribusiness Association of Iowa (-1465), Hawaii Crop Improvement Association (-2196), Western Processors Association (-2198), South Dakota Agribusiness Association (-1625), California Women for Agriculture (-1012), Minnesota AgriGrowth Council (-1671), Agricultural Retailers Association (-1874), Northeast Agribusiness and Feed Alliance (-1879), National Council of Farmer Cooperatives (-2003), Kansas Agribusiness Retailers Association (-1616), Western Growers (-2128), Washington Friends of Farms & Forests (-1002),
 - ii. Alfalfa/Forage: Nebraska Alfalfa Marketing Association (-1222), National Alfalfa and Farm Alliance (-1633), Midwest Forage Association (-1635),
 - iii. Grains: North Dakota Grain Growers Association (-1674), Idaho Grain Producers Association (-1819), Virginia Grain Growers Association (-1672), National Association of Wheat Growers (-2129), Virginia Grain Producers Association (-1672),
 - iv. Corn: Illinois Corn Growers Association (-1642), Iowa Corn Growers Association (-1630), National Corn Growers Association (-2009), South Dakota Corn Growers Association (-1802), Wisconsin Corn Growers Association (-2095), Indiana Corn Growers Association (-2186),
 - v. Cotton: Plains Cotton Growers, Inc. (-0475), Georgia Cotton Commission (-1001), California Cotton Ginners & Growers Association (-2197), National Cotton Council (-1627),

- vi. Soybean: Minnesota Soybean Growers Association (-1006), American Soybean Association (-0943), Kentucky Soybean Association (-1606), Iowa Soybean Association (-1662), Ohio Soybean Association (-1604), North Dakota Soybean Growers Association (-0951),
- vii. Sugar: Western Sugar Cooperative (-0944), American Crystal Sugar Company (-2164), Beet Sugar Development Foundation (-0957), American Sugarbeet Growers Association (-1016), Amalgamated Sugar Company (-1667),
- viii. Specialty Crops: Malheur County Onion Growers Association (-2163), Almond Alliance of California (-1875), Northwest Horticultural Council (-1670),
- c) Non-profit organizations: Center for Food Safety (-2209)
- d) Federal, State or Local Government: Nebraska Department of Agriculture (-2008), Texas Department of Agriculture (-2002, -2018), USDA-Office of Pest Management Policy (-1618)
- e) Agricultural Businesses: Hemdale Farms, Inc. (-1010), Mount Vineyards (-0945), Tri County Ag, LLC (-0957), Agrineed Inc. (-1663),
- f) Pesticide Registrants: Monsanto Company (-1610, -1638)
- g) Farm Bureaus: Illinois Farm Bureau (-1018), American Farm Bureau Federation (-1668), Delaware Farm Bureau (-1669), Kansas Farm Bureau (-1007), Hawaii Farm Bureau (-1872), Arizona Farm Bureau Federation (-1870), Pennsylvania Farm Bureau (-2098), Illinois Farm Bureau (-1605), Idaho Farm Bureau Federation (-1624), Missouri Farm Bureau Federation (-1643), Washington Farm Bureau (-1614), New York Farm Bureau (-2191), Oregon Farm Bureau Federation (-2103)

Summary of Comments on the General Benefits and Use of Glyphosate:

The Agency received comments from a broad range of stakeholders that attested to the general benefits of glyphosate's agricultural and non-agricultural uses. The majority of these comments contained information on the diverse benefits of the use of glyphosate which, according to stakeholders, include: environmental benefits due to glyphosate's role in no-till farming and conservation tillage and reduced carbon emissions, cost-effective and broad spectrum weed control, reduction in management time and farm inputs such as labor and fuel, simplification of weed control programs, better weed control resulting in higher yields, use of fewer and less toxic herbicides, and more flexibility in timing of application.

EPA's Response:

The EPA appreciates the many comments from stakeholders that describe glyphosate's benefits for agricultural and non-agricultural uses. The Agency agrees that glyphosate has the one of the largest pest spectrums of all herbicides and is registered on more use sites than any other herbicide. This is one reason that glyphosate is the preferred option to other herbicides and weed control methods. The Agency also recognizes the crop safety that glyphosate provides. The Agency has not carried out assessments of herbicides replaced by glyphosate but agrees that it is likely that the use of glyphosate results in the replacement of other herbicides and reduces grower inputs.

Summary of Comments on the Benefits and Use of Glyphosate on Glyphosate-Resistant Field Crops

Many commenters provided input concerning the benefits of glyphosate for weed control in glyphosate-resistant (GR) field crops. There are varieties of corn, sweet corn, soybeans, cotton, sugar beets, canola and alfalfa that are resistant to glyphosate. GR varieties comprise large majorities of the acres of field corn, soybeans, cotton and sugar beets produced in the United States. An important advantage of growing GR crops is that glyphosate can be applied directly over the crop canopy without injuring the crop. Commenters also provided information related to GR alfalfa and canola.

The benefits of glyphosate in GR crops cited by commenters include:

- Simplifying weed control:
 - Glyphosate is non-selective. It controls a wide range of broadleaf weeds and grasses.
 - It allows flexibility in timing of weed control. In GR crops, because it can be applied over the canopy, glyphosate can be used at almost any time during the growing season.
 - Glyphosate reduces or eliminates the need for other weed control methods, including other herbicides, many of which pose more risk to humans or the environment.
- It is cost-effective and efficient. Glyphosate can reduce the need for other weed control measures. It can also reduce the number of tractor trips across a field needed for weed control which reduces fuel consumption and labor.
- Facilitating no-till or conservation tillage production of GR crops which reduces or eliminates reliance on tillage for weed control. This results in conserving soil moisture and maintaining soil “health” by reducing soil compaction from tractor trips over the field. No-till and conservation tillage crop production also reduces soil erosion from wind and water and conserves soil moisture.
- In addition to the general benefits to GR crops cited above, comments from sugar beet producers, processors, and related stakeholders indicated that there are specific advantages of glyphosate use on GR sugar beets:
 - Sugar beet growers grow glyphosate-resistant varieties exclusively; it is not possible to produce sugar beets without glyphosate.
 - Prior to the availability of GR sugar beets, growers typically used a weed control program that combed 13 different herbicides. This weed control system required precise timing of applications, specialized equipment, multiple cultivations, and expensive hand labor.
 - Since the introduction of GR sugar beets in 2008, yields have increased by 30 percent.

EPA’s Response:

The Agency appreciates the information provided and agrees that the comments received on this topic point to important benefits of glyphosate and the reasons that its use is often preferred to other weed control practices in GR crops. The Agency cannot confirm any comments related to

quantitative benefits (e.g., yield increases) because quantitative analyses were not conducted by the Agency.

When used on crops genetically-engineered to be glyphosate-resistant, glyphosate is particularly important. Its broad spectrum of weed control (broadleaf weeds and grasses) is likely to reduce farm inputs by reducing the number of herbicides and the number of trips over the field for weed control or tillage. This, in turn, is likely to result in lower labor and fuel costs compared to other weed control systems. Moreover, the Agency agrees that there are benefits in weed control efficiency and to the environment when no-till or conservation tillage, which are facilitated by glyphosate, are part of the production systems in GR field crops. The environmental benefits of no-till or conservation tillage compared to conventional tillage include reduced potential for soil erosion and preservation of soil moisture. Gains in weed management cost and efficiency compared to conventional weed management are realized through reduced trips over the field and savings on fuel and labor.

Although the Agency agrees that the use of glyphosate on GR crops provides benefits to growers, widespread use of and over-dependence on glyphosate for weed control has led to major weed resistance problems, particularly in GR crops. Widespread weed resistance has reduced some of the benefit of glyphosate use in GR crops which detracts from the simplicity of using glyphosate alone for weed control. Resistance has increased reliance on more diverse methods of weed control. In some cases, this includes tillage. It may also include reliance on herbicides other than glyphosate, including the use of pre-emergence herbicides and adding herbicides with a different mechanism of action to tank mixes with glyphosate.

Summary of Comments on Herbicide Resistance

In addition to comments on usage and benefits, there were also comments indicating that widespread use of glyphosate has resulted in increases in weed resistance, particularly in GR crops. Commenters noted that there are 17 weed species in 38 states with documented resistance to glyphosate. Commenters also noted the widespread adoption of GR plants has contributed to the evolution of herbicide resistance. Other stakeholders mentioned that glyphosate is still effective on weeds that are resistant to other herbicides, such as acetolactate synthase inhibitors (ALS herbicides). Other commenters indicated that herbicide-resistant crop technology has led to a major increase in herbicide use in the United States.

EPA Response:

The Agency published two Pesticide Registration Notices (PRNs) which address pest resistance management. PRN 2017-1 (<https://www.epa.gov/pesticide-registration/prn-2017-1-guidance-pesticide-registrants-pesticide-resistance-management>) promotes mechanism of action labeling by pesticide registrants. PRN 2017-2 (<https://www.epa.gov/pesticide-registration/prn-2017-2->

[guidance-herbicide-resistance-management-labeling-education](#)) provides specific guidance for managing herbicide resistance.

Whenever an herbicide is used there is a potential for that use to contribute to the evolution of herbicide resistance, particularly if a weed species or population is subjected to repeat sublethal doses. This may occur in genetically-engineered crops, conventional crops, or non-crop situations. Genetically-engineered crops can be a solution to resistance or exacerbate resistance depending on herbicide use and stewardship within those crops. In the case of glyphosate-resistant crops, over reliance on glyphosate used alone has made glyphosate resistance the worst herbicide resistance problem (Heap, 2014). Glyphosate remains a valuable tool because it is still effective on many populations of weeds including species that have shown resistance to other herbicides. To facilitate management of herbicide resistance, EPA encourages tank-mixing herbicides, promotes diversity in weed control practices, rotating different mechanisms of action, crop rotation, and encourages integrated pest management (IPM) programs. To facilitate adoption of resistance management, the Agency has for several years worked closely with stakeholder groups to promote good resistance management practices. To maintain some of the most important benefits of glyphosate, growers must use the herbicide responsibly as part of an integrated weed control strategy and be proactive in employing good resistance management practices.

In regards to herbicide resistance occurring through pollen mediated gene flow from resistant crops to weedy relatives, the United States Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) evaluates this risk in addition to regulating the planting, importation, or transportation of genetically engineered plants pursuant to its authority under the Plant Protection Act (PPA). By regulation, APHIS classifies most GM plants as plant pests or potential plant pests and as "regulated articles." Under the PPA, a regulated article must receive prior approval from APHIS before it is introduced for commercial production by farmers.

Summary of Comments on the Benefits and Use of Glyphosate on Conventional Field Crops

The Agency received many comments related to the benefits of glyphosate on conventional (i.e., non-GR) field crops. The crops mentioned in this group of comments included small grains, sugarcane, sorghum, alfalfa seed production, and others.

Commenters indicated that glyphosate use in conventional field crops provides some of the same benefits identified above that are not specifically related to GR crops, i.e., where non-selective herbicides can be used without injuring the target crop. These benefits include safe and cost-effective broad-spectrum weed control, facilitating weed control in conservation tillage production systems, and flexibility in application timing where a non-selective herbicide can be used.

Some of the specific circumstances where glyphosate is used in non-GR field crops include burn-down and pre-harvest applications for small grains and other conventional field crops. It can also be used to manage cover crops and fallow ground. It has benefits in sugarcane production where it is used as ripening agent and prior to planting in a fallow period.

EPA's Response:

The Agency appreciates the information submitted and agrees that glyphosate provides benefits in non-GR crops as indicated in the comments. Most of the benefits conveyed to growers of non-GR field crops relate to glyphosate's versatility and flexibility. Glyphosate is registered for nearly all field crops and can be used in most circumstances where non-selective weed control is needed. As with its use in GR crops, to maintain its benefits in conventional field crops, glyphosate should be used as part of a diversified weed control system that includes proactive resistance management practices.

Summary of Comments on the Benefits and Use of Glyphosate on Vegetable Crops

Commenters indicated that glyphosate use in vegetable crop production provides some of the same benefits to growers identified above that are not specifically related to GR crops. It is important where non-selective herbicides can be used without injuring the target crop. These benefits include safe and cost-effective broad-spectrum weed control and flexibility in application timing where a non-selective herbicide can be used. Glyphosate use on vegetables is common for weed burn-down before seeds or transplants go into the soil. It is also used around perimeters of vegetable fields.

Some of the specific circumstances where glyphosate is used in vegetable production include burn-down applications and managing cover crops and fallow ground.

EPA's Response:

The Agency appreciates the information submitted and agrees that glyphosate provides benefits to vegetable crop producers. Most of the benefits conveyed to vegetable growers relate to glyphosate's versatility and flexibility. Glyphosate is registered for nearly all vegetable crops and can be used in most circumstances where non-selective weed control is needed, including pre-plant burn-down and weed control around field perimeters. As with its other use categories, to maintain its benefits to vegetable crop growers, glyphosate should be used as part of a diversified weed control system that includes proactive resistance management practices.

Summary of Comments on Benefits and Use of Glyphosate on Tree and Vine Crops

Commenters indicated that glyphosate use in tree and vine crop production provides some of the same benefits to growers identified above that are not specifically related to GR crops. In these crops its primary use is for weed control on orchard and vineyard floors. It is important where non-selective herbicides can be used without injuring the target crop. These benefits include safe and cost-effective broad-spectrum weed control and flexibility in application timing where a non-selective herbicide can be used.

Some of the specific comments received concerned glyphosate's use and benefits to growers of apples, pears and cherries in the Pacific Northwest. Information was also submitted concerning glyphosate use and benefits in almond production. There were also comments on the benefits of glyphosate to producers of wine grapes, including the importance of using dome sprayers to reduce drift.

EPA's Response:

The Agency appreciates the information submitted and agrees that glyphosate provides benefits to producers of orchard and vine crops. Most of the benefits conveyed to these growers relate to glyphosate's versatility and flexibility. Glyphosate is registered for nearly all orchard and vine crops and can be used in most circumstances where non-selective weed control is needed. As with its other use categories, to maintain its benefits to orchard and vine crop growers, glyphosate should be used as part of a diversified weed control system that includes proactive resistance management practices.

Summary of Comments Regarding the Usage

A number of private citizens expressed concerns that EPA did not adequately assess the large volume of glyphosate use and the large number of use sites as part of registration review. Some commenters, such as Center for Food Safety (CFS), requested that EPA update or adjust usage reports to more accurately depict the scale and trends of agricultural glyphosate usage and overall herbicide usage in the United States.

EPA's Response:

The Agency appreciates these comment regarding usage data. EPA agrees that the overall use of herbicides, in terms of pounds applied, has increased from 2005 to 2016. At various points in registration review, EPA has provided estimates of agricultural usage and non-agricultural for glyphosate. In this assessment, EPA provides an updated summary of glyphosate agricultural usage based on the available agricultural survey data (MRD 2012-2016) at the appropriate geographic and statistically significant scale. EPA also provides an estimates of non-agricultural use data from various sources. The following use reports were previously published in the glyphosate registration review docket: the 2008 *Screening Level Estimates of Agricultural Uses of the Case Glyphosate* and the 2015 *Updated Screening Level Usage Analysis (SLUA) Report for Glyphosate Case PC #s (103601, 103604, 103607, 103608, 103613, 417300)*.

Summary of Comments on Benefits and Use of Glyphosate in Non-Agricultural Scenarios (Forestry, Rights-of-way, Aquatic Uses, etc.)

The Agency received comments from many stakeholders concerning the use and importance of glyphosate in non-agricultural scenarios. Commenters indicated that glyphosate provides some of the same benefits in non-agricultural scenarios that are identified above. It is important where non-selective herbicides can be used and provides flexibility and safe and cost-effective broad-spectrum weed control.

Comments indicated that glyphosate is an important and effective herbicide in a variety of non-agricultural situations. It is useful in vegetation management along roadsides and helps make roads safer (e.g., by improving visibility for drivers). It is also useful in weed control in parks and other public spaces such as school yards, city landscapes and nature trails. It is used to manage turf in commercial areas and golf courses. It is used widely in forest management, particularly for reforestation and to control invasive species. Glyphosate is important to landscape contractors, lawn care specialists, and to nursery and greenhouse managers. Glyphosate is also commonly used for weed control in aquatic systems where it is effective against emerged and floating weeds.

The U.S. Department of Agriculture (USDA) provided information from the U.S. Forest Service (USFS) on situations when relatively high rates of glyphosate are needed for weed control in specific non-crop scenarios. For instance, the Southern USFS region uses glyphosate at rates from 0.2 pounds acid equivalent (lbs. a.e.) per acre to 7.5 lbs. a.e. per acre. The higher end of the rate range is used on “rare” occasions. The scenarios where glyphosate is used at higher rates by the USFS in the Southern region include forest site preparation, invasive plant treatment in forests, administrative sites, rights-of-way, forest nurseries, and creation of wildlife openings (areas cleared of forest canopy and managed as wildlife feeding areas). For the Intermountain and Northern USFS regions, high rates of glyphosate are used for wipe-on, stem wick, cut stem pour application to apply glyphosate selectively and effectively. For the Pacific region, USDA provided information from the Forest Service Activity Tracking System (FACTS) from 1998-2016 showing that the average application rate of glyphosate used for site preparation or conifer release is 2.4 lbs. a.e. per acre.

EPA's response:

The Agency thanks USDA and other stakeholders for the information submitted concerning the use of glyphosate in a variety of non-agricultural scenarios. The Agency is aware of the broad range of non-agricultural use sites on which glyphosate can be used. The Agency is particularly appreciative of the USDA/USFS information concerning situations where relatively high application rates are needed. This information suggests that relatively high application rates of glyphosate are needed for some forestry and aquatic scenarios and that the application method of many of these high rate applications (e.g., 8 lbs. ae per acre) does not reflect a rate that is applied to an entire acre in some situations.

Comments on Residential Uses

Comments indicated that glyphosate is cost-effective and efficacious. Comments also indicated that residential herbicide products are limited.

EPA's Response:

The Agency thanks commenters for this information. This information reiterates that glyphosate has a broad weed control spectrum and is registered on many sites that include turf, ornamentals, and residential/industrial sites.

CHEMICAL INFORMATION

Glyphosate (N-[phosphonomethyl] glycine) is a 5-Enolpyruvyl-Shikimate-3-Phosphate (EPSP) Synthase Inhibitor (WSSA Group 9) herbicide. Glyphosate was commercialized in 1974 and use increased substantially after glyphosate-resistant crops were introduced in 1996. It is the only herbicide with this Mechanism of Action. Glyphosate is absorbed across the leaves and stems of plants and is translocated throughout the plant. It concentrates in meristematic tissue.

Glyphosate can be used as an herbicide or harvest aid. There are numerous salt, amine and ester forms of glyphosate (as noted with the PC Codes above) undergoing registration review. In this document, “glyphosate” is used to describe all forms of glyphosate undergoing review.

Glyphosate controls emerged weed species. It is applied preemergence to crops, and preemergence and early/late postemergence to the crop in GR cropping systems. It is also applied as a fall burndown application to control weeds that emerge after a crop has been harvested. Fall burndown applications help to reduce weed pressure in the following spring.

In addition to agricultural uses, glyphosate is used to control weeds and woody species in residential, non-agricultural and industrial use sites. It can be applied to foliage or cut stems/stumps.

USE AND USAGE

Glyphosate is the most used herbicide in United States’ crop production in terms of acres treated (MRD, 2012-2016). There are approximately 280 million pounds of glyphosate applied to 298 million acres annually in agricultural settings (MRD, 2012-2016). Tables 1a-c present usage information for crops with the greatest usage, in terms of acres treated and pounds applied, for agricultural crops: field crops, orchards and vineyards, and vegetable crops. Table 2 presents the usage information available to the Agency for non-agricultural sites.

The highest potential ecological risks from the use of glyphosate are associated with sites with high maximum application rates, such as pastures, non-food tree crops, forestry, and non-crop uses with application rates at or above 8 lbs. acid equivalence per acre (a.e./acre). There are also potential ecological risks associated with aerial applications and multiple applications of glyphosate.

Agricultural Usage Information

Table 1a summarizes the usage of glyphosate in field crops for the years 2012-2016. Large field crops, with millions of acres planted, such as soybeans, corn, cotton, and sugar beets have the highest total area treated (TAT) and pounds applied with glyphosate (MRD, 2012-2016). The majority of glyphosate use, in terms of total acres treated, occurs late postemergence to the crop

in field crops (MRD, 2012-2016). On average, eighty-four percent of glyphosate, in terms of pounds, is applied to soybeans, corn, or cotton per year (MRD, 2012-2016). These three field crops all have glyphosate-resistant (GR) varieties that have been widely adopted. Many field crops, with and without GR varieties, have a high percentage of their acres treated with glyphosate which is an indication that growers experience benefits from use of this chemical. The field crops with the highest percentage of their acres treated with glyphosate are sugar beets, soybeans, cotton, and corn, respectively (Table 1a). With the exception of sugarcane, the average single application rate for field crops ranges from 0.72 to 1.00 lbs. a.e./acre (Table 1a). With the exception of sugarcane, the average cost per application for field crops ranges from \$3-\$5/acre (Table 1a).

There is also use of glyphosate as a plant growth regulator (PGR) on a few crops. However, sugarcane is the only crop with substantial use of glyphosate as a PGR, with over 50,000 pounds applied to over 254,000 acres (MRD, 2012-2016). Sugarcane has the highest average application rate and per acre cost of glyphosate as an herbicide for field crops at 1.76 lbs. a.e./acre and \$9/acre (Table 1a), which are the second highest overall for all agricultural crops, right behind table grapes (MRD, 2012-2016). Glyphosate usage as a PGR has the lowest average application rate and cost at 0.20 lbs. a.e./acre and \$1, respectively (Table 1a).

Table 1a. Average Annual Glyphosate Usage in Agricultural Crops- *Field Crops*, 2012-2016

Crop¹	Total Area Treated (acres)	Pounds (lbs.) Acid Equivalent (a.e.) Applied	Single Application Rate (lbs. a.e./acre)	Number of Applications	Percent Crop Treated (PCT)	Cost (\$) /TAT
Barley	1,102,000	800,000	0.72	1.2	29%	\$3
Canola (oilseed rape) ⁴	1,237,000	835,000	0.67	1.6	57%	\$3
Corn ⁴	100,196,000	94,909,000	0.95	1.3	80%	\$5
Cotton ^{3,4}	20,215,000	20,115,000	1.00	2.2	89%	\$5
Dry Beans/Peas	1,762,000	1,356,000	0.76	1.3	44%	\$3
Peanuts	452,000	407,000	0.90	1.1	29%	\$4
Potatoes ³	150,000	135,000	0.89	1.0	14%	\$5
Rice	1,482,000	1,432,000	0.96	1.2	46%	\$5
Sorghum	6,095,000	5,097,000	0.83	1.6	53%	\$4
Soybeans ⁴	117,400,000	113,937,000	0.97	1.6	92%	\$5
Sugar Beets ⁴	2,608,000	2,449,000	0.94	2.3	98%	\$4
Sugarcane (H) ³	249,000	410,000	1.76	1.2	24%	\$9
Sugarcane (PGR) ³	254,000	52,000	0.20	1.0	30%	\$1
Sunflowers	1,772,000	1,413,000	0.80	1.4	74%	\$3
Wheat, Spring	7,060,000	5,312,000	0.75	1.2	41%	\$3
Wheat, Winter	8,373,000	6,814,000	0.81	1.1	20%	\$4

Fallow ²	16,752,000	13,263,000	0.79	1.9	64%	\$3

MRD 2012-2016

1 - There were 11 crops in the MRD that showed less than 10% of the crop treated with glyphosate: alfalfa, artichoke, carrots, cauliflower, celery, garlic, lettuce, lima beans, pastureland, spinach, and tobacco. Taken together, the total average annual pounds of glyphosate used on these 11 crops was approximately 2 million lbs. or less than 1% of the total use of glyphosate on all surveyed crops. These crops are not listed in the table.

2 - Fallow land- land going coming out of production or ready to go back into production, but not crop specific and typically associated with grain production.

3- There are a few crops with recent PGR (plant growth regulator) use of glyphosate: cotton, potatoes and sugarcane. However, since sugarcane was the only one with significant and consistent use, it is included in this table. The (H) stands for herbicide use in sugarcane. To get the total use in terms of pounds or acres treated, it would be necessary to add these two sugarcane rows together.

4- Crops with substantial acreage planted with glyphosate-resistant varieties.

Many citrus fruits (e.g. grapefruit, oranges, lemons) and tree nuts (e.g. almonds, walnuts, pistachios) have the highest percentage of their acres treated with glyphosate. As with field crops, a high PCT is indicative of benefits to growers of those crops. The orchard and vineyard crops with the highest percentage of their acres treated with glyphosate are grapefruit, oranges, almonds, and grapes, respectively (Table 1b).

Most orchard/vineyard crops have average single application rates around 1.00 lb. a.e./acre (Table 1b). However, grapes (table and wine) and grapefruit have average application rates above 1.50 lbs. ae/acre (Table 1b). The average cost per application for orchard/vineyard crops ranges from \$5-\$13/acre (Table 1b). The average number of applications ranges from 1 to 3 applications per year (Table 1b). Generally, the average number of applications (~2) in orchard and vineyard crops is higher than for field crops or vegetables (~1) (MRD 2012-2016).

Table 2b. Average Annual Glyphosate Usage in Agricultural Crops - *Orchards and Vineyards*, 2012-2016

Crop ¹	Total Area Treated (acres)	Pounds (lbs.) Acid Equivalent (a.e.) Applied	Single Application Rate (lbs. a.e./acre)	Number of Applications	Percent Crop Treated (PCT)	Cost (\$) /TAT
Almonds	2,174,000	2,138,000	0.99	2.5	89%	\$6
Apples	275,000	220,000	0.82	1.5	58%	\$5
Apricots	13,000	10,000	0.90	1.9	62%	\$5
Cherries	162,000	158,000	1.00	1.5	76%	\$6
Grapefruit	205,000	313,000	1.56	3.5	93%	\$7
Grapes, Raisin	263,000	346,000	1.31	1.6	74%	\$8
Grapes, Table	196,000	359,000	1.84	2.0	88%	\$13
Grapes, Wine	735,000	1,190,000	1.62	1.6	74%	\$10
Hazelnuts	22,000	24,000	1.11	1.2	50%	\$6
Lemons	121,000	173,000	1.42	2.6	78%	\$10
Oranges	2,074,000	2,697,000	1.31	3.5	91%	\$7
Peaches	123,000	115,000	0.95	2.1	58%	\$5
Pecans	429,000	342,000	0.80	2.7	34%	\$4
Pistachios	560,000	561,000	1.00	2.6	84%	\$6
Plums/Prunes	150,000	145,000	1.00	2.3	81%	\$6

Walnuts	602,000	590,000	0.98	2.2	82%	\$6

MRD 2012-2016

The TAT and pounds applied for vegetables and fruits (i.e. those listed in Table 1c), is lower than for the previously mentioned groups of agricultural crops. This is mostly driven by the fact that the average acre and field size of these crops is lower than that of typical field or orchard/vineyard crops. As with field and orchard/vineyard crops, a high PCT is indicative of benefits to growers of these crops.

The vegetable and fruit crops with the highest percentage of their acres treated with glyphosate are asparagus, cucumbers, onions and tomatoes, respectively (Table 1c). Sweet corn and succulent beans are also vegetable crops with high TAT and pounds applied (Table 1c). The average single application rate for vegetables ranges from 0.89 to 1.73 lbs. a.e./acre (Table 1c). The average cost per application for vegetables ranges from \$5-\$8/acre (Table 1c). The average number of applications for each vegetable crop is less than 1.5 applications per year (Table 1c).

Table 3c. Average Annual Glyphosate Usage in Agricultural Crops - *Vegetables and Other Crops*, 2012-2016

Crop ¹	Total Area Treated (acres)	Pounds (lbs) Acid Equivalent (a.e.) Applied	Single Application Rate (lbs. a.e./acre)	Number of Applications	Percent Crop Treated (PCT)	Cost (\$) /TAT
Asparagus	23,000	22,000	0.99	1.5	60%	\$5
Cabbage	14,000	23,000	1.55	1.2	20%	\$8
Caneberries	5,000	5,000	0.89	1.7	13%	\$5
Cantaloupes	8,000	14,000	1.64	1.1	13%	\$8
Cucumbers	40,000	56,000	1.40	1.2	30%	\$6
Onions	51,000	52,000	1.03	1.2	34%	\$5
Peppers	17,000	25,000	1.47	1.1	22%	\$7
Pumpkins	16,000	19,000	1.22	1.1	19%	\$7
Squash	13,000	18,000	1.38	1.0	28%	\$7
Strawberries	11,000	21,000	1.73	1.5	13%	\$7
Succulent Beans	53,000	72,000	1.34	1.1	21%	\$6
Succulent Peas	25,000	23,000	0.89	1.0	15%	\$5
Sweet Corn	140,000	166,000	1.17	1.1	26%	\$6
Tomatoes	134,000	158,000	1.17	1.2	34%	\$7
Watermelons	25,000	27,000	1.17	1.2	17%	\$6

MRD 2012-2016

1 - There were 11 crops in the MRD that showed less than 10% of the crop treated with glyphosate: alfalfa, artichoke, carrots, cauliflower, celery, garlic, lettuce, lima beans, pastureland, spinach, and tobacco. Taken together, the total average annual pounds of glyphosate used on these 11 crops was approximately 2 million lbs. or less than 1% of the total use of glyphosate on all surveyed crops. These crops are not listed in the table.

Applications Methods for Glyphosate

There are many ways of applying glyphosate; methods of application include aerial, ground, spot treatments, strip sprays, trunk sprays, etc. BEAD only has data on application methods for agricultural sites. Ground is by far the most common application method with over 90% of acres (or 284 million acres) being treated in this way (MRD, 2012-2016). Despite the variety of application methods, the average rates per method are still around 1 lbs. a.e./acre, ranging from 0.92 lbs. a.e./acre for ground to 1.39 lbs. a.e./acre for trunk sprays. (MRD, 2012-2016)

Aerial is not a common application method for agricultural users of glyphosate. This application method represents about 2% (or 5 million) of all acres treated with glyphosate (MRD, 2012-2016). The crop sites with the largest number of acres treated with aerial applications are soybeans, corn, cotton, and rice, respectively, which altogether account for over 4 million of the 5 million acres treated aerially (MRD, 2012-2016). The crops with the highest percentage of their acres treated aerially with glyphosate are rice (36%) and tomatoes (8%). The average rate for aerial applications is 0.98 lbs. a.e./acre. (MRD, 2012-2016).

Application Rates for Glyphosate

With the high PCT, acres treated, and pounds applied with glyphosate for many crops (Tables 1a-c), glyphosate use is prevalent nationwide. The benefits of glyphosate are described in subsequent sections of this memo. In addition to benefits, there are also ecological risks, primarily driven by repeated applications at maximum crop cycle rates and for non-agricultural use sites or spot treatments where the maximum annual rate or single application rate is high. Typically, the maximum labeled single application rate for most uses is lower than 8.00 lbs. a.e./acre. Generally, the label maximum is 3.75 a.e./acre or less for ground applications (inclusive of most GR crops such as corn, cotton, and sugar beets) and 1.55 a.e./acre or less for aerial applications. As noted earlier, the average rates as shown in Tables 1a-c are typically around 1.00 lbs. a.e./acre. Approximately 90% of ground applications to agricultural sites occur at or below 2.00 lb. a.e./acre and around 90% of aerial applications of glyphosate to agricultural use sites occur at or below 1.25 lb. a.e./A (MRD, 2012-2016).

Non-Agricultural Usage Information

Approximately 24 million pounds of glyphosate were reported as being used in 2011 on a variety of non-agricultural sites (Kline, 2012a and b). Glyphosate is usually one of the top chemical control options for these sites. Glyphosate was the most used herbicide in terms of pounds in the consumer market (e.g. homeowners) (Kline, 2012a). The consumer market, turf, and forestry sites had the highest use of glyphosate in terms of pounds applied (Table 2). Glyphosate was the most used herbicide for roadways in terms of acre-treatments and the Agency received comments supporting the benefits of this use pattern (Kline, 2012b). It was the second most used herbicide, in terms of acre-treatments, for electric utilities and pipelines, forestry, and railroad use sites (Kline, 2012b). In 2011, glyphosate accounted for 7% of all herbicide acre-treatments for control of aquatic vegetation (Kline, 2012b). The Florida Fish and Wildlife commission applied over 40,000 pounds of glyphosate in aquatic settings in 2017 (FWC, 2017). Glyphosate was the fourth most-used active

ingredient, in terms of acres treated, applied by the United States Forest Service to control invasive weeds in 2013 (USFS, 2013). Nationally, glyphosate is the leading active ingredient applied by federal entities for the control of invasive species (Wagner et al., 2017).

Table 2. Annual Glyphosate Usage for Non-Crop Sites, 2011

Use Site	Pounds Applied (Lbs. a.e.)	Acre Treatments
Aquatic	128,900	40,000
Consumer Market ¹	5,000,000	-
Electric Utilities and Pipelines (Rights of Way)	2,070,200	654,000
Forestry	3,646,900	757,000
Nursery Greenhouse	2,800,000	-
Railroads (Rights of Way)	528,000	293,000
Range and Pasture	1,479,000	1,498,000
Roadways	3,271,000	1,833,000
Turf ²	4,920,000	-
Total	23,844,000	-

Kline 2012a and Kline 2012b

¹ This site includes use by homeowners.

² This site “turf” includes institutional turf (e.g. cemeteries and parks) (59%), lawn care operators (20%), landscape professionals (12%), golf courses (7%), and turf (2%).

BEAD does not have detailed application rate data for the sites listed in Table 2.

According to comments from the United States Department of Agriculture (USDA), application to these use sites with higher rates (e.g. aquatic, forestry, rights of way) are generally done via handheld, wick, wipe-on, brush-on, and other equipment that are unlikely to contribute to non-target exposure.

BENEFITS OF GLYPHOSATE

Glyphosate is a relatively inexpensive herbicide for agricultural applications (MRD, 2012-2016) that provides control of numerous broadleaf weeds, sedges, and grasses. In addition to the broad-spectrum of pests controlled, it has few use restrictions and can be used immediately before planting in many crops and in non-agricultural sites. Generally, in the absence of glyphosate, users would need to change to active ingredients that have more stringent use restrictions, narrower control spectrums, or mechanical methods. Some of these methods may not be as cost-effective.

Field Crops

Glyphosate is used at various crop timings in a large variety of field crops throughout the United States. Glyphosate can be applied for post-harvest fall burndown, preplant burndown, at plant weed control, over-the-top weed control (in GR crops), directed spot treatments, between row

weed control, and as a harvest aid. A majority of canola, corn, cotton, sorghum, and soybean acres (over 50 percent of acres treated by crop [Table 1]) are treated at least once each year; while other crops such as barley, rice, peanuts, and wheat also have substantial percentages (>20 percent) of acres treated each year (MRD, 2012-2016). The average single application rate for most of these crops does not exceed 1.0 lbs. per acre. The average number of applications in most field crops is between 1 and 2 applications, with two exceptions: cotton and sugar beets. Cotton is treated 2.2 times, on average, and sugar beet is treated 2.3 times, on average (MRD, 2012-2016).

Glyphosate-Resistant Field Crops

Current glyphosate-resistant field crops include soybean, corn, cotton, canola, alfalfa, and sugar beet. Many of these crops, such as corn, cotton, soybean, and sugar beet, have exceptionally high percentages of their acreage treated with glyphosate (approximately 90 percent of acres treated in each crop [Table 1]). GR canola is also available, and canola also has a high PCT (57 percent) (MRD, 2012-2016). Genetically-engineered (transgenic) glyphosate-resistant (GR) varieties of these crops can be sprayed over-the-top with minimal or no crop phytotoxicity, and glyphosate may also be used as a pre-plant burndown in many of these crops. For example, the Iowa Corn and Soybean Production guide (Owen, 2019) recommends 14 postemergence herbicide products in soybean. Only three of the active ingredients in these products control broadleaf and grass species: glyphosate, imazamox, and imazethapyr. Of these three active ingredients, only glyphosate has an excellent crop safety rating (for GR varieties) (Owen, 2019). The widespread use of glyphosate in GR systems is attributed to simplicity and cost efficiency (Powles, 2008). Without access to glyphosate, growers of GR field crops would convert to other herbicides with corresponding resistant crop varieties (if available) or change to other chemical or mechanical practices to control weeds. Given that glyphosate is relatively inexpensive at \$3 to \$5 per acre (Table 1a), these alternative methods of control could lead to increases in cost for these users of glyphosate.

GR alfalfa is also available; however, average PCT for alfalfa is less than 5 percent (MRD, 2012-2016).

Non-glyphosate Resistant Field Crops

Glyphosate is also used in field crops that are not glyphosate-resistant for early season weed control (burndown), termination of cover crops, and as a harvest aid. For example, glyphosate is used as an herbicide on high percentages of barley, peanut, rice, sorghum, sunflower, spring wheat, and winter wheat acres (PCTs ranging from 29 percent to 74 percent) (MRD, 2012-2016). Glyphosate controls a broad spectrum of weeds and has a short plant-back interval; therefore, growers can apply a burndown application and plant a sensitive crop within a few days or weeks. These characteristics of glyphosate also support no-till or strip-till production. The adoption of cover crops varies widely by geographic region and crop, but if a grower planted a cover crop, glyphosate may also be used to terminate the cover crop before planting the subsequent crop. When used as a harvest aid, glyphosate can control green weeds and accelerates uniform maturity in cereals such as wheat, corn, barley, oats, and sorghum.

Non-GR corn, cotton, and soybean, which make up small percentages of national acreages, are also treated with glyphosate for burndown prior to planting. On average, GR corn, cotton and

soybean receive more applications of glyphosate than non-GR corn, cotton, and soybean (MRD, 2012-2016). For example, GR cotton receives an average of 2 applications while non-GR cotton receives 1 application on average (MRD, 2012-2016). Average rates in non-GR corn, cotton, and soybean are similar to GR corn, cotton and soybean (approximately 1.0 lb. per acre) (MRD, 2012-2016). Without access to glyphosate or with restriction(s) that severely limit the use parameters of glyphosate, growers of non-GR field crops would change to other chemical or mechanical practices to control weeds. Given that glyphosate is relatively inexpensive, at \$3 to \$5 per acre (Table 1a), these alternative methods of control could lead to increases in cost for these users of glyphosate. Depending on the crop, other broad-spectrum burndown herbicides for non-GR varieties could include paraquat and glufosinate and broadleaf specific herbicides such as 2,4-D, or dicamba combined with other active ingredients. In other cases, no-till growers may resort to tillage.

Orchards and Vineyards

Weeds impact production in orchards and vineyards by competing with trees and vines, inhibiting irrigation, and acting as habitat for a variety of insect pests (Mitchem, 2016; Washington State University, undated). Orchard floor management helps to control erosion, limit rodent populations, and increase harvest efficiency. Generally, the orchard floor is divided into two areas: the area directly beneath the trees and the area between trees rows which may be planted in a cover crop or sod. Depending on the crop, glyphosate can be used to manage plants in the row-middles, to manage weeds in the row, or to establish a vegetation free orchard floor for crop harvest.

Glyphosate is used in the establishment of orchards or vineyards and used to control weeds once established. Glyphosate may also be used for chemical mowing or wiping. Chemical mowing is the application of sub-lethal rates of an herbicide to reduce the number of times a sod strip needs to be mowed throughout the season. Chemical wiping is an application method through which taller weeds are contacted with glyphosate without disturbing desirable sod (University of Florida, 2018). Glyphosate is the only nonselective postemergence systemic herbicide recommended for use in citrus (University of Florida, 2016). It is the most diverse herbicide in orchard floor management because it may be used for under tree weed control, chemical wiping, chemical mowing, and spot treatment. Non-selective chemical control of weeds could be achieved with paraquat or glufosinate or a combination of broadleaf and grass products (University of Florida, 2016.)

Orchard crops and vineyards have very high percentages of acres treated with glyphosate (Table 1b). Almonds, walnuts, pistachios, and plums/prunes all have over 80 percent of their acres treated with glyphosate. Oranges and grapefruit each have over 90 percent of their acres treated. Table grapes, wine grapes, and raisin grapes have over 80 percent of their acres treated, as well. Generally, orchards and vineyards receive more applications than field crops with most of these perennial cropping systems averaging 2 to 3.5 applications. For example, oranges receive an average of 3.5 applications and table grapes receive an average of 2 applications. The average single application rate in tree nuts and stone fruit is approximately 1.0 lbs. per acre, while average single application rates in grapes and citrus are approximately 1.5 lbs. per acre (Table 1b).

Glyphosate is typically the leading herbicide in orchard floor management because of its broad-spectrum, versatility of use, and cost. For example, glyphosate is the leading herbicide applied in

tree nuts (almonds, hazelnuts, pecans, and pistachios, walnut), vineyards, and in citrus, in terms of TAT (MRD, 2012-2016). The next four leading active ingredients in tree nuts are oxyfluorfen, saflufenacil, paraquat and indaziflam (MRD, 2012-2016). Of these, saflufenacil, oxyfluorfen, and paraquat are recommended for control of emerged weeds (UC-IPM, 2017). Paraquat is a restricted use product; certain oxyfluorfen formulations have restricted use periods in California due to air quality concerns (CDPR, 2015); and all three herbicides have longer re-entry intervals (REIs) than glyphosate (UC-IPM, 2017).

Glyphosate is also the leading herbicide in citrus (grapefruit, lemons, and oranges), in terms of TAT (MRD, 2012-2016). The next four leading herbicides are diuron, indaziflam, 2,4-D, and saflufenacil (MRD, 2012-2016). Indaziflam and diuron are preemergence, residual herbicides, while 2,4-D and saflufenacil can be applied to control emerged weeds but only control broadleaf weeds (University of Florida, 2018). Diuron and indaziflam can be tank mixed with postemergence herbicides to control of weeds that have not yet germinated; however, there are many options for preemergence herbicides in orchards. Glyphosate is non-selective; therefore, it can fulfill the need to control both grasses and broadleaf weeds after they have emerged. In addition, glyphosate has other advantages in that its use is not typically restricted (e.g. due to being a restricted-use product (RUP), like paraquat, or having state level restrictions, like oxyfluorfen). It has short REIs so growers and their workers can re-enter fields more quickly. This reduces interference with necessary in-field activities like scouting. Other broad-spectrum, postemergence herbicides recommended for orchards include paraquat and carfentrazone, both of which are contact and require good coverage to be effective (University of Florida, 2016).

For weed management in vineyards, glyphosate is the leading herbicide, followed by oxyfluorfen, paraquat, glufosinate, and carfentrazone-ethyl (in terms of TAT) (MRD, 2012-2016). Carfentrazone only controls broadleaf weeds and paraquat, glufosinate, and oxyfluorfen all have longer REIs than glyphosate (UC-IPM, 2016a).

Without access to glyphosate or with restriction(s) that severely limit the use parameters of glyphosate, growers of orchard and vineyard crops would change to other chemical or mechanical practices to help with orchard/vineyard establishment, to chemically mow or wipe, and/or to control weeds. Given that glyphosate is relatively inexpensive, \$5 to \$13 per acre for orchard/vineyard crops, these alternative methods could lead to increases in cost for these users of glyphosate. In addition, some alternative chemical methods of control have additional restrictions, (e.g. such as being partially off-labelled in some states, needing special certifications for use [i.e. RUP] or having longer REIs) that may restrict their use.

Vegetables and Other Crops

Many vegetables and other crops (listed in Table 1c.) have substantial portions of their acreage treated each year with glyphosate. One of the major uses of glyphosate is as a burndown herbicide application. Burndown applications are made post-harvest to prevent weed seed production or before planting, so that a grower can plant into a vegetation-free field to eliminate early season weed competition for the crop as it emerges. The majority of glyphosate applied in vegetables, in terms of TAT, is applied at pre-plant or pre-transplant (approximately 75 percent of total acres treated) (MRD, 2012-2016). Glyphosate is the leading herbicide active ingredient applied to

vegetables and cucurbits pre-plant or pre-transplant (MRD, 2012-2016). The next five-leading active ingredients for this timing include metolachlor-S, trifluralin, pendimethalin, oxyfluorfen, and imazethapyr (MRD, 2012-2016). These five alternatives are used primarily when glyphosate use is not appropriate, e.g., when growers make herbicide applications to prevent weed seed germination or when glyphosate use would result in crop damage.

There is a GR sweet corn variety available and twenty-five percent of sweet corn acres are treated with glyphosate (MRD, 2012-2016). However, like other vegetables, most glyphosate is used prior to planting (MRD, 2012-2016) for burndown. Glyphosate is also used from planting to emergence in vegetables, as 15 percent of glyphosate TAT in vegetables occurs during this period (MRD, 2012-2016). Glyphosate is also labeled for shielded or hooded sprayer applications in row middles and wiper application in row middles.

In cole crops, artichokes, asparagus, and leafy vegetables, glyphosate is the fifth-leading herbicide used, in terms of total acres treated (MRD, 2012-2016). The majority of acres treated with glyphosate occur pre-plant or pre-transplant or after planting until emergence (MRD, 2012-2016). The four herbicides with more acres treated for all timings are pronamide, bensulide, oxyfluorfen, and DCPA (MRD, 2012-2016). Pronamide, bensulide, and DCPA are all used to prevent weeds from emerging. While oxyfluorfen is used after the crop and weeds emerge. Glyphosate is the second-leading foliar active ingredient used in cole crops (MRD, 2012-2016). In cucurbits, the top five leading herbicides, in terms of TAT, are ethalfluralin, clomazone, glyphosate, halosulfuron, and trifluralin (MRD, 2012-2016).

Overall, glyphosate is the predominate herbicide used at burndown in vegetable production because it is effective on a wide range of weed species, affordable, easy-to-use, and does not have residual phytotoxicity. Glyphosate is also used from planting to emergence in vegetables.

Although it may not be the market-leading or first-choice herbicide option in all crops, it is a top option for growers for reasons similar to those of the burndown vegetable users (e.g. affordable, broad-spectrum). Without access to glyphosate or with restriction(s) that severely limit the use parameters of glyphosate, growers of some vegetable and fruit crops would change to other chemical or mechanical practices to control weeds or for burndown applications. Given that glyphosate is relatively inexpensive, \$5 to \$8 per acre for these crops, these alternative methods could lead to increases in cost for these users of glyphosate, especially for burndown.

NON-CROP SITES

Pasture and Rangelands

Western rangelands are disturbed environments that are vulnerable to encroachment of invasive weeds. DiTomaso (2010) estimates that encroaching vegetation leads to a loss of \$5 billion annually in the United States. The loss was attributed to lower yields and quality of forage resulting in slowed weight gain of cattle, illnesses and deaths associated with toxic plants, increased production costs, reduced quality of animal products (e.g., meat, hides), and reducing the value of land. However, Duncan et. al. (2004) mentions that the economic impacts are often poorly documented and do not account for “non-market costs such as those to society and the environment (e.g., changes in fire frequency, wildlife habitat, aesthetics, biodiversity).”

Duncan et al. (2004) reviewed 16 invasive plants that were selected based on their infestation level and perceived environmental or economic impact. These 16 plants infest more than 120 million acres of land in the United States. Most of the weeds impact the community structure of the ecosystem by one of several means (e.g., reducing forage and wildlife habitat, displacing native species, altering the soil) (DiTomaso, 2010).). Glyphosate controls 13 of the 16 invasive weeds (musk thistle [*Carduus nutans*], Russian knapweed [*Acroptilon repens*], diffuse knapweed [*Centaurea diffusa*], spotted knapweed [*Centaurea maculosa*], yellow starthistle [*Centaurea solstitialis*], Canada thistle [*Cirsium arvense*], leafy spurge [*Euphorbia esula*], purple loosestrife [*Lythrum salicaria*], saltcedar [*Tamarix ramosissima*], medusahead [*Taeniatherum caput-medusae*], perennial pepperweed [*Lepidium latifolium*], *Sericea lespedeza* [lespedeza]).

Rights-of-Way

Rights-of-way vegetation control can be broken into 4 major categories: roadside, electrical lines, pipelines and railroads, which cover more than 20 million acres of land in the United States (NRCA, 2006). Well maintained rights-of-way are important to the economy because they are critical to the distribution of goods and services. Safety is also a major driver for vegetation control. Vegetation control along roadsides increases visibility, enhances drainage, prevents erosion and degradation of road surfaces, prevents the spread of invasive species, and reduces the potential for fires and snow drift. Weed control provides railroads with many of the same benefits roadside weed control including good visibility for drivers, engineers and inspector, drainage, erosion and fire control, protection of railroad, and safe work areas in rail yards. Vegetation management for electric utilities and pipelines provides workers safe surfaces while working, makes doing inspections easier, and prevents overgrowth of vegetation from interfering with infrastructures. Glyphosate applications can control vegetation under a wide variety of mixed species and site conditions.

Forestry

Land managers use forestry herbicides to increase forest productivity and achieve management goals. Silvicultural objectives include: forest stand improvement, precommercial thinning, site preparation, release operations, and invasive plant control (Penn State University, 2016). Glyphosate provides forest and timber managers with a versatile and cost-effective tool to control unwanted vegetation (Oregon State University, 2014). The Forest Service uses glyphosate primarily for conifer release, site preparation, and noxious weed control (USDA Forest Service, 2011). Other management objectives for which glyphosate is used by the Forest Service include, wildlife habitat improvement, grassland restoration, and reduction of fuels for fire management (USDA Forest Service, 2011). Application rates in forestry settings are generally higher than most agricultural applications due to target species being woody species or species that are difficult to control. For example, from 2000-2004 the average application rate across all Forest Service regions from was 2.07 lbs. ae per acre, while some regions such as the Pacific Southwest have average rates as high a 3.75 lbs. a.e. per acre (USDA Forest Service, 2011). Conifer release treatments had the one of the highest average rates per acre, at 3.21 lbs. a.e. per acre (USDA Forest Service, 2011).

Aquatic Systems

In aquatic systems, invasive weeds can alter the plant and animal species richness and abundance have cascading ecological effects by depleting oxygen levels in water and altering food webs (Hussner et al. 2017). Additionally, aquatic weeds can hinder commerce and navigation, degrade water for recreational activities (e.g., water sports, fishing), decrease property values, clog hydropower dams (and thereby reducing generation of power) and surface water intakes, and reduce water flow in irrigation and drainage systems (e.g., Hussner et al. 2017).

Glyphosate is an important herbicide for aquatic weed managers because it controls a broad spectrum of annual and perennial broadleaf weeds and grasses, trees, and certain floating plants. The Florida Fish and Wildlife Conservation Commission reported use of glyphosate for emergent species such as *Typha* species (bulrush and cattail), floating species such as *Nymphoides cristata* (Crested floating heart), and for woody species such as *Salix spp.* (willow), among other nuisance aquatic species (FWC, 2017). Unlike triclopyr and imazapyr (other systemic aquatic herbicides that control emergent vegetation), glyphosate does not have irrigation water use restrictions. Some of the most invasive floating and emerged weeds controlled by glyphosate are waterfern (*Azolla filiculoides*), water hyacinth (*Eichhornia crassipes*), floating pennywort (*Hydrocotyle ranunculoides*), giant salvinia (*Salvinia molesta*), and water primrose (*Ludwigia spp.*) (Hussner et al. 2017, and references within).

Residential Uses

There are numerous products containing glyphosate that are available for residential uses. Glyphosate is the market leader for the consumer herbicide market (Kline 2012a). Additionally, this market segment was the largest non-agricultural use in terms of pounds (Table 2).

Glyphosate accounted for roughly 40% of consumer herbicides pounds sold in 2011 (5.1 million as shown in Table 2), followed by 2,4 D with about 20% (2.3 million pounds), and MCPA with 10% (1.3 million pounds) (Kline, 2012a). Glyphosate is the most widely used active ingredient in nonselective herbicides and accounts for almost 70% of total active ingredient pounds sold (Kline, 2012a). According to the consumer market for pesticides report, “Consumer interest in glyphosate-based nonselective vegetation control herbicides continues to be strong due to their effectiveness, their reputation for safety, the increasing popularity of spot-treatment of weeds, and stronger promotion for edging, maintenance of paved areas, and other applications.” (Kline, 2012a) Additionally, glyphosate is usually listed as an herbicide control option for homeowners in university extension recommendations and other sources in the open literature geared towards educating homeowners about pesticides (Langeland 2003, McCullough et al, 2015, and UMD, undated). Typically, glyphosate is described in their documents or websites as an herbicide that is “non-selective and giv[es] broad-spectrum control of many annual weeds, perennial weeds, woody brush and trees” (McCullough et al, 2015).

Turf

Turf refers to grass grown for production (seed or sod), golf courses, athletic fields, etc. The turf category in Table 2 also includes use by professional groundskeepers in residential areas. The turf category was also the second largest non-agricultural use in terms of pounds (Table 2). Weed control may impact yield and/or seed/turf quality, or it may be primarily driven by aesthetics. Most perennial grass weeds cannot be controlled with selective herbicides without damage to the turf.

Glyphosate may be used prior to planting turf for site preparation or for spot treatment control of perennial grasses and sedges in existing lawns (UC-IPM, 2016). Spot treatment with a nonselective herbicide such as glyphosate is an effective way to control perennial grasses without leaving harmful soil residuals which slow down the growth of replacement plants or turfgrass. Glyphosate may also be used to control broadleaf weeds and grasses when applied to dormant desirable turf (Penn State, 2018).

ADDITIONAL BENEFITS OF GLYPHOSATE: GENERAL CONTROL OF INVASIVE SPECIES

Invasive plant species are detrimental to the economy and environment of the United States. Impacts from invasive species include:

- Direct competition with native plant species can result in the decline of threatened and endangered species;
- Reductions in plant diversity;
- Degradation of wildlife habitat;
- Reductions in agricultural land quality;
- Degradation of water quality;
- And decreased opportunities for recreation (USDA-Forest Service, undated; Invasive Species Advisory Committee, 2006).

Wagner et al. (2016) compiled information from numerous federal sources to determine herbicide usage for invasive species control and found that, from 2007-2011, approximately 2.5 million acres of wildland were sprayed with an assortment of sixty-five herbicides. The leading sites for application included grasslands, road maintenance, and forest sites. Nationally, glyphosate was leading active ingredient in terms of amount applied and area treated (Wagner et al., 2016). The next most-used active ingredients, in terms of total area treated, were triclopyr, imazapyr, and clopyralid. Glyphosate's popularity in invasive species management may be attributed to its broad spectrum, low mobility and half-life in soil, and low toxicity for wildlife when compared to alternatives (Duke and Powles, 2008). Further, glyphosate may be more affordable than other active ingredients. Controlling woody species may require high application rates of glyphosate and rely on application methods such as stem injection, wiping, and stump treatments.

GLYPHOSATE RESISTANCE

Over the last 20 years, herbicide resistance has increased at a rate of 13 new unique cases annually at a global level (Heap, 2018). Currently, there is a total of 79 unique cases of weed species that are resistant to one or more different herbicide modes of action (MOA) in the United States. There are 35 weed species that are resistant to more than one MOA and there are 17 weeds that have at least one case of multiple resistance (i.e., the population of weeds is resistant to multiple herbicides across different MOA). Even though industry is working on developing new herbicides, there are no herbicides with a new MOA that will be available in the near future (Sparks and Lorschbach 2016). Herbicide resistant weeds have become a significant financial, production, and pest management issue for many herbicide users in the United States.

There are 17 weed species in the United States that have developed resistance to glyphosate (Heap, 2018). The first glyphosate-resistant species in the United States (ryegrass) appeared in California in 1998 (Heap, 2018). Glyphosate-resistant weed populations appeared quickly after the deregulation and adoption of GR crops, and they were also found in perennial cropping systems such as orchards (Duke and Powles, 2008). Herbicide-resistance technology allows multiple applications of the same active ingredient for longer periods of time (e.g., corn soybean glyphosate-resistant crop rotation), which substantially increases selection pressure. Glyphosate resistance first appeared in Roundup Ready (RR) soybeans in 2001. In 2005, glyphosate resistant Palmer amaranth appeared in numerous southern states (Heap, 2018). Of these glyphosate resistant weeds, many are difficult-to-control or common in agricultural systems and non-crop systems (Van Wyken, 2016; 2017).

Glyphosate resistance can decrease the benefits of glyphosate to users if resistance is so prevalent that: 1) a grower must resort to mechanical removal of glyphosate-resistant biotypes (i.e. tilling or chopping) 2) a grower must tank mix other active ingredients with glyphosate in order to control glyphosate-resistant biotypes, 3) a grower must change active ingredients in order to control glyphosate resistant biotypes, or 4) a grower must grow another less profitable crop.

IMPACTS OF POSSIBLE PROPOSED SPRAY DRIFT MITIGATION

While there are no human health risks of concern associated with glyphosate use, there are environmental risks of concern. There are risks to birds, non-target plants, and mammals associated with the use of glyphosate. The Agency is considering implementing mitigation to reduce these risks.

Temperature Inversions

The Agency is considering adding label language preventing applications during temperature inversions. This requirement could reduce the amount of time users have to apply glyphosate. Users may switch to other products that do not have this restriction if they encounter temperature inversions.

Release Height

The Agency is considering a maximum release height of 10 feet for aerial applications, with exceptions for reasons of pilot safety, and a release height of 4 feet or less for ground boom applications.

EPA does not anticipate that these release heights will impact the use of glyphosate because applications at these heights are standard practice.

Droplet Size

The Agency is considering requiring a fine or coarser droplet size for all ground and aerial broadcast applications.

EPA does not anticipate that applying fine or coarser droplets will affect the efficacy of glyphosate when glyphosate is used alone since it is systemic. Extension specialists estimate that more than 80% of applicators apply herbicides in tank mixes (Sprague 2018, Steckel 2018) because it allows growers to control herbicide resistant weeds, broadens the spectrum of weeds controlled, delays the development of resistant weeds, saves time and resources with one trip across the field (Sprague, 2018) and reduce rates (Culpepper and York 2018). Glyphosate is a compound that is frequently tank mixed with other herbicides. Because the proposed language provides flexibility with droplet size for tank mixed partners, BEAD does not expect there would be concerns for tank mixes with other herbicides. However, since glyphosate is commonly applied as a burndown treatment, insecticides may be included in the tank mix. Insecticides are generally considered to provide better efficacy with smaller droplets such as fine droplets. BEAD does not know if requiring fine droplets will impact the efficacy of insecticides tank mixed with glyphosate because some insecticides could be more effective at droplet sizes smaller than fine (such as very fine or extremely fine). If reduced efficacy occurred, BEAD would expect growers to respond by increasing the application rates (if allowed by the label), increasing the number of applications, increasing the application rates of tank mix partners, making additional applications, or switch to a different active ingredient.

Wind Speed

The Agency is considering 15 mph maximum wind speed for ground and aerial applications. For aerial applications, the Agency is considering the following language:

Do not apply when wind speeds exceed 15 mph at the application site. If the wind speed is greater than 10 mph, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor blade diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.

Most labels currently have restrictions of 10 mph for maximum wind speed. This language should provide more flexibility to applicators who are willing to change the boom length in conditions above 10 mph.

CONCLUSIONS

Glyphosate is a broad-spectrum herbicide that is applied on an average to 298 million acres of crop land annually, making it the most commonly used herbicide on agricultural sites in the United States. It is also the most commonly used herbicide by pounds in the consumer or residential use market and for the control of invasive weeds. It controls most broadleaves, sedges, and grasses and is labeled for use on most agricultural and non-agricultural use sites. It is also relatively inexpensive in agricultural settings, ranging \$1 per acre to \$13 per acre across all agricultural use sites.

Glyphosate can be applied for post-harvest fall burndown, preplant burndown, at plant weed control, over-the-top weed control (in GR crops), directed spot treatments, between row weed control, and as a harvest aid. Approximately one-half of agricultural acres are treated with applications that are applied late postemergence (to the crop). Removal of weeds at late

postemergence is important to reduce competition nutrient, sunlight, and water, and to eradicate habitat for insect pests. Pre-plant applications of glyphosate are also important to growers who practice conservation tillage, so that they can continue this practice. Other benefits of glyphosate include few use restrictions and minimum residual phytotoxicity, so desirable vegetation can be planted soon after applications occur.

Glyphosate is used to control weeds in non-agricultural and industrial use sites. Glyphosate is important for noxious weed control in aquatic systems, pastures/rangelands and right-of-way applications. Glyphosate is the top active ingredient used to control invasive species in the United States.

There are currently 17 weed species that are resistant to glyphosate in the United States. Glyphosate resistance can reduce the benefit of glyphosate to users if resistance is so prevalent that they must change to alternative weed control options that could be more expensive or less effective. Despite widespread resistance, glyphosate remains a valuable tool for controlling both herbicide resistant and non-herbicide resistant weeds.

Potential spray drift management measures being considered include changes to boom length, wind speed, droplet size and release height for aerial applications. The Agency is also considering restricting applications during temperature inversions. Restrictions during temperature inversions may impact the usability of glyphosate products; however, most spray drift management measures are not expected to substantially reduce the benefit of glyphosate to users.

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Exhibit 13

Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential

**EPA's Office of Pesticide Programs
December 12, 2017**



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List of Acronyms

ADME: Absorption, Distribution, Metabolism, and Excretion
AHS: Agricultural Health Study
AOP: Adverse Outcome Pathway
AMPA: Aminomethylphosphonic Acid
BrdU: Bromodeoxyuridine
CA: Chromosomal Aberration
CARC: Cancer Assessment Review Committee
CBPI: Cytokinesis Block Proliferation Index
CHL: Chinese Hamster Lung
CHO: Chinese Hamster Ovary
CPRC: Carcinogenicity Peer Review Committee
EFSA: European Food Safety Authority
EPSPS: 5-enolpyruvylshikimate-3-phosphate synthase
FAO: Food and Agriculture Organization
FIFRA: Federal Insecticide, Fungicide, and Rodenticide Act
FISH: Fluorescence *in situ* Hybridization
GC-MS: Gas Chromatography-Mass Spectrometry
HL: Hodgkin Lymphoma
HPLC: High-Performance Liquid Chromatography
HPRT: Hypoxanthine-Guanine Phosphoribosyl Transferase
IARC: International Agency for Research on Cancer
JMPR: Joint FAO/WHO Meeting on Pesticide Residues
MGUS: Monoclonal Gammopathy of Undetermined Significance
MN: Micronuclei
MOA: Mode of Action
MPCE: Micronucleated Polychromatic Erythrocytes
MRID: Master Record Identifier (a unique number assigned to each study submitted to EPA)
MTD: Maximum Tolerated Dose
NB: Nuclear Bud
NCR: National Research Council
NHL: Non-Hodgkin Lymphoma
NPB: Nucleoplasmic Bridges
NTP: National Toxicology Program
OCSPP: Office of Chemical Safety and Pollution Prevention
OECD: Organization for Economic Cooperation and Development
OPP: Office of Pesticides Program
PCE: Polychromatic Erythrocytes
PK: Pharmacokinetic
PPE: Personal Protective Equipment
PWG: Pathology Work Group
RED: Registration Eligibility Decision
ROS: Reactive Oxygen Species
SAP: Scientific Advisory Panel
SCE: Sister Chromatid Exchange

SCGE: Single Cell Gel Electrophoresis
TAC: Total Antioxidant Capacity
TK: Thymidine Kinase
UDS: Unscheduled DNA Synthesis
USGS: United States Geological Survey
UV: Ultraviolet
WHO: World Health Organization
XPRT: Xanthine-Guanine Phosphoribosyl Transferase

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1.0 Introduction

1.1 Background

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. The herbicide acts by inhibiting the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme, which is not present in mammalian systems. Glyphosate was initially registered in 1974. Since then, several human health analyses have been completed for glyphosate. In 1986, EPA issued the Glyphosate Registration Standard which updated the agency's toxicity database for this compound. In 1993, EPA issued the registration eligibility decision (RED) that indicated that glyphosate was eligible for re-registration.

Currently, glyphosate is undergoing Registration Review¹, a program where all registered pesticides are reviewed at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The initial docket opening for glyphosate occurred in 2009 with the publication of the human health scoping document and preliminary work plan². As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health. Risks are assessed using current practices and policies to ensure pesticide products can still be used safely. Registration Review also allows the agency to incorporate new science. For human health risk assessment, both non-cancer and cancer effects are evaluated for glyphosate and its metabolites, aminomethylphosphonic acid (AMPA) and *N*-acetyl-glyphosate; however, this document will focus on the cancer effects only. EPA expects to complete its complete human health risk assessment in 2017 that will include an assessment of risk from anticipated exposures resulting from registered uses of glyphosate in residential and occupational settings.

1.2 Evaluation of Carcinogenic Potential

Since its registration, the carcinogenic potential of glyphosate has been evaluated by EPA several times. In 1985, the initial peer review of glyphosate was conducted in accordance with the Proposed Guidelines for Carcinogen Risk Assessment. The agency classified glyphosate as a Group C chemical (Possible Human Carcinogen), based on the presence of kidney tumors in male mice. In 1986, the agency requested that the FIFRA Scientific Advisory Panel (SAP) evaluate the carcinogenic potential of glyphosate. The panel determined that the data on renal tumors in male mice were equivocal (only an increase in adenomas was observed and the increase did not reach statistical significance). As a result, the panel recommended a Group D chemical classification (Not Classifiable as to Human Carcinogenicity) for glyphosate and advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify the unresolved questions (FIFRA SAP Report, 1986)³.

¹ Additional information on the Registration Review process can be found at: <https://www.epa.gov/pesticide-reevaluation/registration-review-process>

² Documents of the Registration Review can be found in the public docket at: EPA-HQ-OPP-2009-0361, accessible at www.regulations.gov.

³ Review available at: http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

With the submission of two rat carcinogenicity studies following this data call-in, a second peer review was conducted in 1991 by the agency's Carcinogenicity Peer Review Committee (CPRC) to incorporate the new data. In accordance with the agency's 1986 Draft Guidelines for Carcinogen Risk Assessment, the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Most recently, in September 2015, a third review was done by the Cancer Assessment Review Committee (CARC). Relevant glyphosate data available to EPA at that time for glyphosate were reevaluated, including studies submitted by the registrant and studies published in the open literature. The agency performed this evaluation in support of Registration Review in accordance with the 2005 Guidelines for Carcinogen Risk Assessment, classified glyphosate as "Not Likely to be Carcinogenic to Humans" (CARC, 2015; TXR #0057299).

In recent years, 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), determined that glyphosate was a probable carcinogen (group 2A) (IARC, 2015). Later, in November 2015, the European Food Safety Authority (EFSA) determined that glyphosate was unlikely to pose a carcinogenic hazard to humans (EFSA, 2015). 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 (JMPR, 2016). Some individual countries in Europe (e.g., France, Sweden) have considered banning glyphosate uses based on the IARC decision, while other countries (e.g., Japan, Canada, Australia, New Zealand) have continued to support their conclusion that glyphosate is unlikely to pose a carcinogenic risk to humans.

The recent peer review performed by CARC served as an initial analysis to update the data evaluation for glyphosate at that time. Based on an evaluation of the studies included in the recent analyses by IARC, JMPR, and EFSA, the agency then became aware of additional relevant studies not available to EPA. As a result, EPA also requested information from registrants about studies that existed, but had never been submitted to the agency. The current evaluation incorporates these additional studies. In addition, the agency conducted a systematic review of the open literature and toxicological databases for glyphosate by using a "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment". As such, the current evaluation also provides a more thorough evaluation than the 2015 CARC review.

In December 2016, the FIFRA SAP was convened to evaluate the agency's Issue Paper regarding the human carcinogenic potential of glyphosate. The panel's report was published in March 2017 and the current document incorporates revisions based on the panel's report (G. Akerman; 12-DEC-2017; TXR#0057689). Additionally, information from a recently published analysis of glyphosate use and cancer incidence in the Agricultural Health Study (AHS) cohort (Andreotti et al., 2017) with a longer follow-up than the previously published data (De Roos et al., 2005) has been considered in this evaluation.

1.3 Overview of “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment”

In 2010, the Office of Pesticide Programs (OPP) developed a draft “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment” which provides the foundation for evaluating multiple lines of scientific evidence in the context of understanding of the mode of action (MOA)/adverse outcome pathway (AOP) (U.S. EPA, 2010). The draft framework, which includes two key components, problem formulation and use of the MOA/AOP pathway frameworks, was reviewed favorably by the FIFRA SAP in 2010 (FIFRA SAP, 2010). In 2016, a final version of the framework was published⁴, which incorporated improvements based on recommendations from the SAP, public comments, and the experience gained since 2010 conducting assessments on several pesticides for which epidemiological data were available. Recently, EPA has applied this framework to the evaluation of atrazine and chlorpyrifos⁵.

OPP’s framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety MOA/human relevance framework, which highlights the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek *et al.*, 2014). Consistent with recommendations by the National Research Council (NRC) in its 2009 report on *Science and Decisions*, OPP’s framework describes the importance of using problem formulation at the beginning of a complex scientific analysis. The problem formulation stage starts with planning dialogue with risk managers to identify goals for the analysis and possible risk management strategies. This initial dialogue provides the regulatory context for the scientific analysis and helps define the scope of such an analysis. The problem formulation stage also involves consideration of the available information regarding the pesticide use/usage, toxicological effects of concern, and exposure pathways and duration along with key gaps in data or scientific information. Specific to glyphosate, the scoping document prepared for Registration Review (J. Langsdale *et al.*, 2009) along with the review conducted by the CARC (CARC, 2015) represent the problem formulation analyses for the weight-of-evidence evaluation for carcinogenic potential. A summary of the US exposure profile is provided in Section 1.4 to provide context for interpreting the various lines of evidence.

One of the key components of the agency’s framework is the use of the MOA framework/AOP concept (Figure 1.1) as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies. Specifically, the modified Bradford Hill Criteria (Hill, 1965) are used to evaluate strength, consistency, dose response, temporal concordance and biological plausibility of multiple lines of evidence in a weight-of-evidence analysis.

⁴ <https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf>

⁵ Chlorpyrifos Revised Human Health Risk Assessment for Registration Review; 29-DEC-2014; D424485. U.S. EPA 2010 SAP Background White Paper – Re-evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. EPA-HQ-OPP-2010-0125. U.S. EPA 2011 SAP Issue Paper – Re-evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. EPA-HQ-OPP-2011-0399.

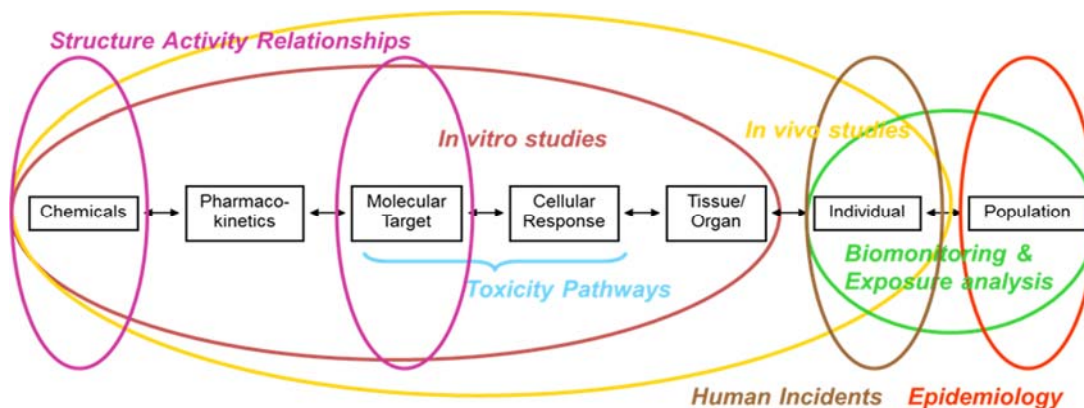


Figure 1.1. Source to outcome pathway (adapted from NRC, 2007).

1.4 Summary of the Exposure Profile in the United States

All pesticide products provide critical information about how to safely and legally handle and use pesticide products. Pesticide labels are legally enforceable and all carry the statement “it is a violation of Federal law to use this product in a manner inconsistent with its labeling.” In other words, the label is law. As a result, a key function of the pesticide product label is to manage the potential risk from pesticides.

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. It is also registered for use on glyphosate-resistant (transgenic) crop varieties such as corn, soybean, canola, cotton, sugar beets, and wheat. Registered tolerances in the United States include residues of the parent compound glyphosate and *N*-acetyl-glyphosate, a metabolite found in/on glyphosate-tolerant crops⁶.

Dietary (food and water) exposures are anticipated from applications to crops. Since there are registered uses of glyphosate that may be used in residential settings, residential handlers may be exposed to glyphosate during applications. Exposures may also occur from entering non-occupational areas that have been previously treated with glyphosate. Occupational/commercial workers may be exposed to glyphosate while handling the pesticide prior to application (mixing and/or loading), during application, or when entering treated sites. The agency considers all of the anticipated exposure pathways as part of their evaluation for human health.

Oral exposure is considered the primary route of concern for glyphosate. Oral absorption has been shown to be relatively low for glyphosate (~30% of administered doses) with negligible accumulation in tissues and rapid excretion (primarily unchanged parent) via the urine. Due to its low vapor pressure, inhalation exposure to glyphosate is expected to be minimal. Dermal penetration has also been shown to be relatively low for human skin (<1%) indicating dermal exposure will only contribute slightly to a systemic biological dose. Furthermore, in route-

⁶ All currently registered tolerances for residues of glyphosate can be found in the Code of Federal Regulations (40 CFR §180.364).

specific inhalation and dermal toxicity studies, no adverse effects were observed. This all suggests that there is low potential for a sustainable biological dose following glyphosate exposure.

In residential/non-occupational settings, children 1-2 years old are considered the most highly exposed subpopulation with oral exposures from dietary (food and water) ingestion and incidental oral ingestion (e.g., hand-to-mouth activities) in treated areas. There is also potential for dermal exposures in previously treated areas. Using OPP's standard exposure assessment methodologies which are based on peer-reviewed and validated exposure data and models⁷, a high-end estimate of combined exposure for children 1-2 years old is 0.47 mg/kg/day (see Appendix E).

At the time of initial registration (1974), total use of glyphosate in the United States was approximately 1.4 million pounds (Benbrook, 2016). In 1995, total use of glyphosate increased to approximately 40 million pounds with agriculture accounting for 70% of use. With the introduction of transgenic crop varieties in the United States circa 1996, (such as soybean, cotton, and corn) use of glyphosate increased dramatically (Green and Owen, 2011), and in 2000 the total use of glyphosate in the United States was approximately 98.5 million pounds. By 2014, total annual use of glyphosate was approximately 280-290 million pounds (based on Benbrook, 2016 and industry proprietary data accessible to EPA) with agriculture accounting for 90% of use. Although glyphosate use has continuously increased up to 2012, the stabilization of glyphosate usage in recent years is due to the increase in a number of glyphosate-resistant weed species, starting with rigid ryegrass identified in California in 1998 and currently totaling 16 different weed species in the United States as of March 2016. Figure 1.2 below provides a visual representation of the increased agricultural use of glyphosate in the United States using proprietary market research data from 1987-2014.

The increased use of glyphosate may be partly attributed to an increase in the number of farmers using glyphosate; however, it is more likely that individuals already using glyphosate increased their use and subsequent exposure. With the introduction of transgenic crop varieties, glyphosate use shifted from pre-emergent to a combination of pre- and post-emergent applications. Additionally, application rates increased in some instances and more applications were allowed per year (2-3 times/year). Maps from the United States Geological Survey (USGS) displaying glyphosate use in the United States indicate that although use has drastically increased since 1994, areas treated with glyphosate for agricultural purposes appear to be approximately the same over time (Figures 1.3-1.4). The introduction of transgenic crops in some cases led to a shift in crops grown on individual farms, such that more acreage within the farm would be dedicated to growing the glyphosate-tolerant crops replacing other crops. In addition, during the 2000s there was also an increase in growing corn for ethanol production, which could also have resulted in increased acreage dedicated glyphosate-tolerant corn.

⁷ Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

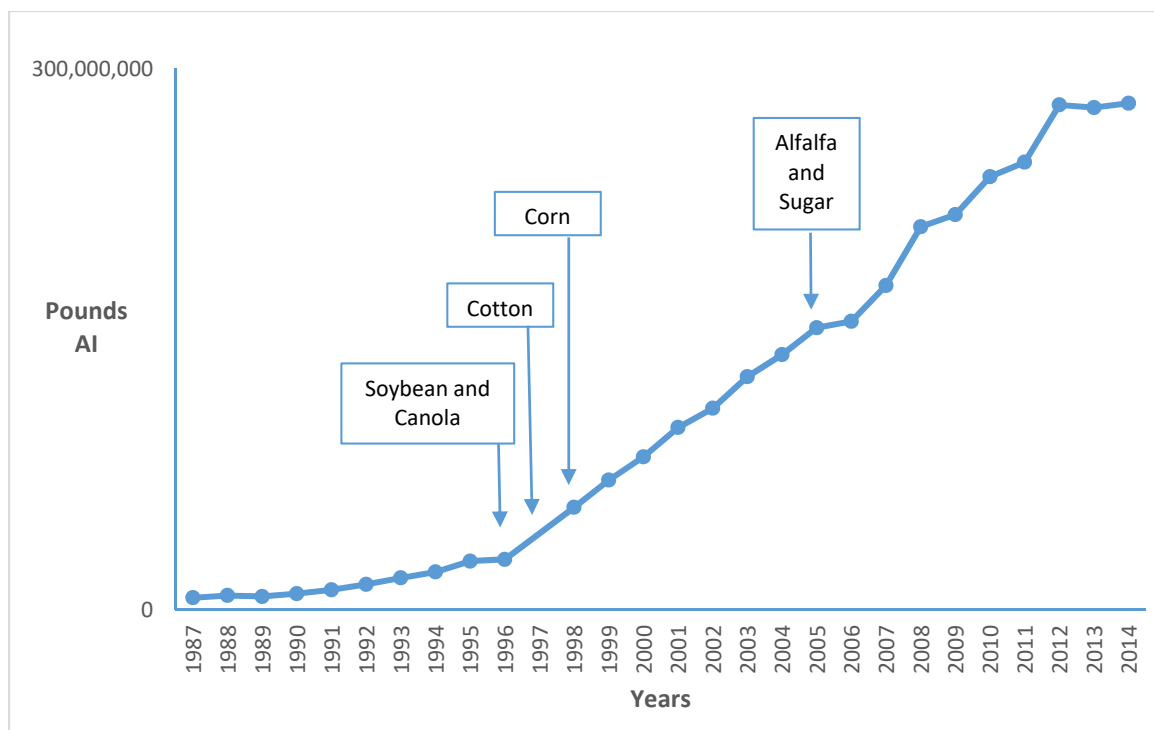


Figure 1.2. Glyphosate agricultural usage (pounds applied annually) from 1987- 2014. Boxes indicate years when glyphosate-resistant crops were introduced. Source: Proprietary Market Research Data (1987 – 2014).

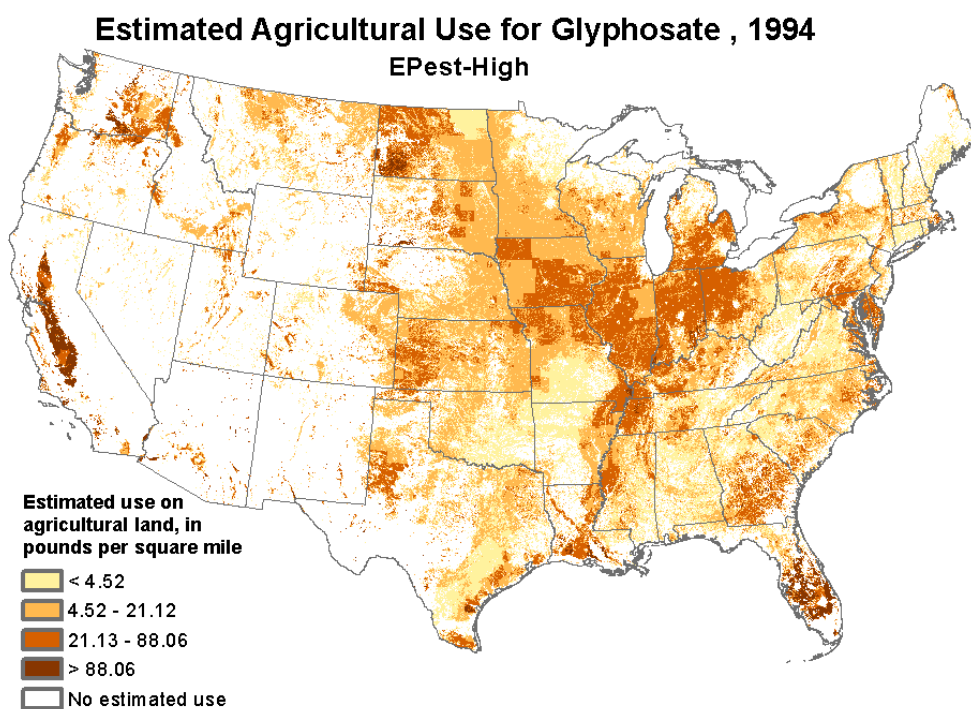


Figure 1.3. Map of estimated agricultural use for glyphosate in 1994 from USGS (http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=1994&map=GLYPHOSATE&hilo=H)

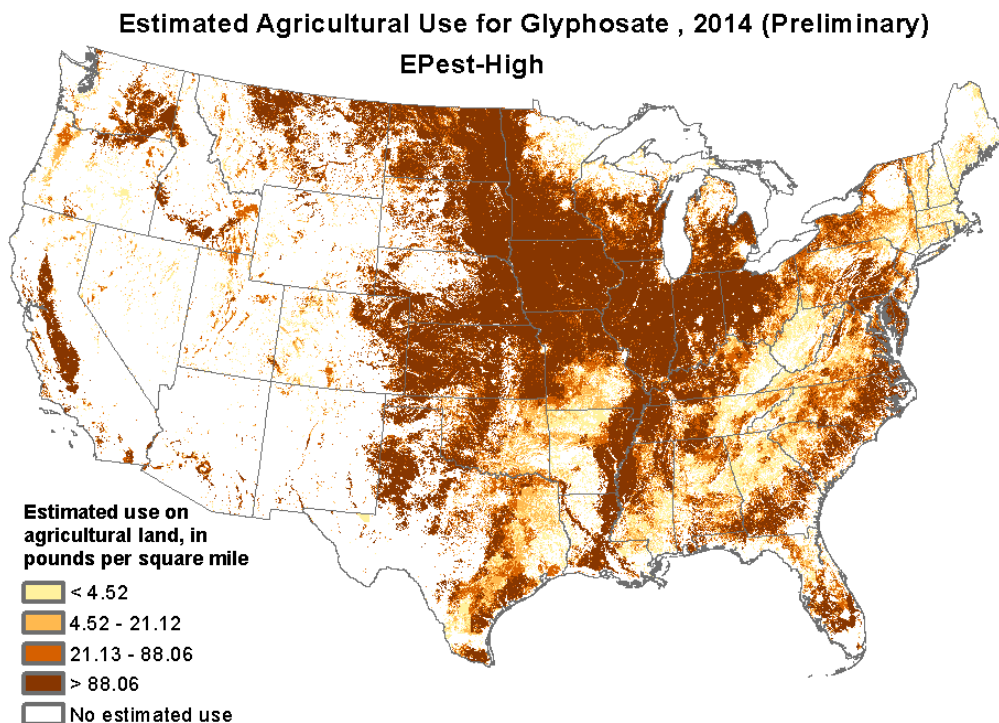


Figure 1.4. Map of estimated agricultural use for glyphosate in 2014 from USGS
(http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2014&map=GLYPHOSATE&hilo=H)

The potential exposure to occupational handlers is dependent on the formulation, specific task (mixer, loader, and/or applicator), rate of application, and acreage treated. Using HED's standard occupational exposure assessment methodologies which are based on peer-reviewed and validated exposure data and models⁸, mixer/loaders result in the highest potential exposure estimates. Assuming no personal protective equipment (PPE), exposure estimates for mixer/loaders range from 0.03-7 mg/kg/day using the maximum application rate for high acreage agricultural crops (6 lb ai/acre)⁹. For applicators, exposure would be lower with estimates ranging from 0.02-0.03 mg/kg/day using the same application rate and acreage.

The maximum potential exposures from currently registered uses of glyphosate in residential and occupational settings in the United States are used in the current evaluation to aid in the determination of whether findings in laboratory studies are relevant for human health risk assessment. In Sections 4.0 and 5.0, descriptions are provided for animal carcinogenicity and genotoxicity studies, respectively. Results from these studies, particularly those administering high doses, are put into context with the human exposure potential in the United States.

⁸ Available: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data>

⁹ Based on use information provided by the Joint Glyphosate Task Force for the following end-use products: EPA Registration Nos.: 100-1182, 228-713, 524-343, 524-475, 524-537, 524-549, 524-579, 4787-23, and 62719-556.

1.5 Organization of this Document

In this analysis of the human carcinogenic potential of the active ingredient glyphosate, the agency has performed a comprehensive analysis of available data from submitted guideline studies and the open literature. This includes epidemiological, animal carcinogenicity, and genotoxicity studies. Consistent with the framework described in Section 1.3, the agency has evaluated these multiple lines of evidence and conducted a weight-of-evidence analysis. Although there are studies available on glyphosate-based pesticide formulations, the agency is soliciting advice from the FIFRA SAP on this evaluation of human carcinogenic potential for the active ingredient glyphosate only at this time. The remainder of this document is organized by the following:

- *Section 2.0 Systematic Review & Data Collection Methods* provides a description of methods used to compile all relevant studies used in the current evaluation.
- *Section 3.0 Data Evaluation of Epidemiology* describes the available epidemiological studies, evaluates relevant studies for study quality, and discusses reported effect estimates.
- *Section 4.0 Data Evaluation of Animal Carcinogenicity Studies* provides a description and evaluation of the available animal carcinogenicity studies for glyphosate.
- *Section 5.0 Data Evaluation of Genetic Toxicity* summarizes and discusses the various genotoxicity assays that have been tested with glyphosate.
- *Section 6.0 Data Integration & Weight of Evidence Analysis Across Multiple Lines of Evidence* integrates available data discussed in Sections 3.0-5.0 to consider concepts, such as strength, consistency, dose response, temporal concordance and biological plausibility in a weight-of-evidence analysis. This section also provides discussion of the data in the context of cancer descriptors provided in the 2005 Guidelines for Carcinogen Risk Assessment.
- *Section 7.0 Collaborative Research Plan for Glyphosate and Glyphosate Formulations* provides a discussion of planned research that is intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity.

2.0 Systematic Review & Data Collection

In recent years, the National Academy of Sciences National Research Council (NRC) has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making (NRC, 2011). The NRC defines systematic review as “a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies” (NRC, 2014). Consistent with NRC’s recommendations, EPA’s Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures. In short, OCSPP employs “fit for purpose” systematic reviews that rely on standard methods for **collecting, evaluating, and integrating** the scientific data supporting the agency’s decisions. The concept of fit for purpose implies that a particular activity or method is suitable for its intended use. Inherent in this definition is the concept that one size does not fit all

situations and thus flexibility is allowed. However, it is notable that with flexibility comes the importance of transparency of documented processes; including the importance of transparency and clarity in approaches to data collection, evaluation, and integration. These are described throughout the document with data collection in Sections 2.1.1-2.1.2, evaluation in Sections 3-5, and integration in Section 6.

As a result, more recent evaluations are starting to reflect this progression in the agency's process. Similar to the framework for incorporating human epidemiologic and incident data, systematic review begins with a problem formulation to determine the scope and purpose of the search. Studies are considered based on their relevance to answer specific questions and those studies deemed relevant are then further considered for their usefulness in risk assessment.

The agency strives to use high-quality studies when evaluating the hazard potential of pesticidal chemicals and considers a broad set of data during this process. This includes registrant generated studies required under FIFRA, as well as peer-reviewed scientific journals and other sources, such as other governments and academia. A wide range of potential adverse effects are assessed using acute, subchronic, chronic, and route-specific studies; predominately from studies with laboratory animals, in addition to epidemiologic and human incident data. All studies are thoroughly reviewed to ensure appropriate conduct and methodologies are utilized, and that sufficient data and details are provided. In this way, hazards are identified and potential risks characterized to ensure that decisions are informed by the best science available.

2.1 Data Collection: Methods & Sources

Data were collected by searching the open literature (Section 2.1.1) and other publicly available sources (e.g., recent internal reviews, evaluations by other organizations) (Section 2.1.2). Internal databases were also searched for submitted studies conducted according to Organization for Economic Cooperation and Development (OECD) test guidelines, OCSPP harmonized test guidelines, and other pesticide test guidelines (OPP guidelines) (Section 2.1.2).

It should be noted that glyphosate is primarily manufactured as various salts with cations, such as isopropylamine, ammonium, or sodium. These salts are derivatives of the active substance glyphosate and increase the solubility of technical-grade glyphosate acid in water. All of these forms were considered for the current evaluation.

2.1.1 Open Literature Search

As part of the evaluation of the human carcinogenic potential of glyphosate, the literature review described here uses concepts consistent with fit for purpose systematic review, such as detailed tracking of search terms and which literature have been included or excluded. The primary goal of the literature search was to identify relevant and appropriate open literature studies that had the potential to inform the agency on the human carcinogenic potential of glyphosate. Therefore, non-mammalian studies were not considered, and several terms were used in the search string in an attempt to exclude non-mammalian studies.

To obtain literature studies, OPP worked with EPA librarians to conduct searches in PubMed, Web of Science, and Science Direct. A search was conducted on May 6, 2016 in PubMed and Web of Science using the following search string to yield 141 and 225 results, respectively:

```
((glyphosate OR "1071-83-6" OR roundup OR "N-(Phosphonomethyl)glycine") AND  
(aneuploid* OR chromosom* OR clastogenic* OR "DNA damag*" OR "DNA adduct*" OR  
genome* OR genotoxic* OR micronucle* OR cancer* OR carcinogen* OR oncogenic* OR  
mutagen* OR cytotoxic* OR tumor* OR tumour* OR malignanc* OR neoplasm* OR *oma))  
NOT (fish* OR frog* OR tadpole* OR insect* OR eco* OR amphibian* OR reptil* OR  
invertebrate* OR fly OR flies OR aquatic OR bird* OR aqueous OR water OR yeast* OR worm*  
OR earthworm* OR bacteria* OR lichen OR resist* OR "herbicide resist")
```

Due to differences with using Science Direct, the search string was slightly changed. This search was also conducted on May 6, 2016 and yielded 459 results:

```
((glyphosate OR "1071-83-6" OR roundup OR "N-(Phosphonomethyl)glycine") AND  
(aneuploid* OR chromosom* OR clastogenic* OR (DNA pre/2 (damag* OR adduct*)) OR  
genome* OR genotoxic* OR micronucle* OR cancer* OR carcinogen* OR oncogenic* OR  
mutagen* OR cytotoxic* OR tumor* OR tumour* OR malignanc* OR neoplasm* OR *oma))  
AND NOT (eco* OR fish* OR frog* OR tadpole* OR invertebrate* OR bird* OR insect* OR fly  
OR flies OR amphibian* OR reptil* OR yeast* OR aquatic OR aqueous OR water OR worm*  
OR earthworm* OR bacteria* OR lichen OR resist* OR "herbicide resist")
```

After cross-referencing the results obtained from the three open literature searches for duplicates, a total of 735 individual articles were obtained (Appendix A) and one additional study (Alvarez-Moya et al., 2014) not identified in the search was added to this list for a total of 736 individual articles. Three staff members independently evaluated all of the studies and came to consensus on which studies would be considered relevant to the issue of concern (i.e., human carcinogenic potential of glyphosate). Many of the articles were not considered to be within the scope of the search or not considered relevant in general (657 articles). Additionally, 27 articles were not appropriate due to the type of article (i.e., correspondence, abstract only, not available in English, retraction). Of the 52 relevant articles, 42 were used in the current evaluation (31 genotoxicity, 9 epidemiological, and 2 animal carcinogenicity). Three articles also reported on the potential of glyphosate and its metabolites to be developed into therapeutic drugs for cancer treatment. The remaining 7 articles evaluated effects on glyphosate or glyphosate formulations on cellular processes, mostly focusing on epidermal cells, and were not considered informative for the current evaluation.

2.1.2 Studies Submitted to the Agency

For all pesticides, there are toxicology data requirements that must be submitted to the agency for registration. These studies, defined under the 40 CFR Part 158 Toxicology Data Requirements, provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and lifestages. They typically follow OECD, OCSPP, or OPP accepted protocols and guidelines, which ease comparisons across studies and chemicals.

The toxicological databases for glyphosate¹⁰ were reviewed and all relevant animal, genotoxicity, and metabolism studies were collected for consideration.

Several resources were used to ensure all relevant studies were included in the current evaluation. The list of studies obtained from the toxicological database and the open literature search were cross-referenced with recent internal reviews (CARC, 2015; S. Recore *et al.*, 2014). This list was also cross-referenced with review articles from the open literature [Chang and Delzell (2016), Greim *et al.* (2015), Kier and Kirkland (2013), Kier (2015), Mink *et al.* (2012), Schinasi and Leon (2014), and Williams *et al.* (2000)]¹¹. EPA requested studies from registrants that were not previously available to the EPA. As a result, numerous studies were subsequently submitted to the agency. Study reports for one animal carcinogenicity study and 17 genotoxicity studies were not available to the agency and have been noted in the relevant sections below. For these studies, data and study summaries provided in Greim *et al.* (2015) and Kier and Kirkland (2013) were relied upon for the current evaluation.

2.2 Evaluation of Relevant Studies

Studies submitted to the agency are evaluating based on OECD, OCSPP, or OPP test guideline requirements to determine whether studies are acceptable for use in risk assessment. In the current evaluation, animal carcinogenicity, genotoxicity, and metabolism studies located in the internal databases with access to full study reports were evaluated in this manner. Those classified as unacceptable were noted and subsequently excluded from the current evaluation.

In order to evaluate open literature studies, criteria described in the OPP guidance for considering and using open literature toxicity studies to support human health risk assessment was utilized (U.S. EPA, 2012). This guidance assists OPP scientists in their judgement of the scientific quality of open literature publications. More specifically, the document discusses how to screen open literature studies for journal articles/publications that are relevant to risk assessment, how to review potentially useful journal articles/publications and categorize them as to their usefulness in risk assessment, and how the studies may be used in the risk assessment. As with submitted studies, those deemed unacceptable were noted and subsequently excluded from the current evaluation.

¹⁰ Glyphosate pesticide chemical (PC) codes: 103601, 103603, 103604, 103605, 103607, 103608, 103613, 128501, and 417300.

¹¹ All review articles, except Schinasi and Leon (2014), were funded and/or linked to Monsanto Co. or other registrants.

3.0 Data Evaluation of Epidemiology

3.1 Introduction

Epidemiological studies are valuable for risk assessment since they may provide direct evidence on whether human exposure to a chemical may cause cancer. Studies of high quality and adequate statistical power are preferable and remove the need to account for extrapolation from animals to humans or extrapolation from high to low doses. Epidemiological studies can also be integrated with experimental evidence when determining or clarifying the carcinogenic potential of a chemical for risk assessment. The key considerations in evaluating epidemiologic studies are study design, exposure assessment, outcome assessment, confounding control, statistical analyses, and risk of other bias.

OPP routinely evaluates the available epidemiological literature. As part of Registration Review of glyphosate, an evaluation was initially conducted in 2014 (S. Recore *et al.*, 2014) and subsequently another evaluation was performed in 2015 (CARC, 2015). The 2015 evaluation began with the epidemiological studies previously identified in the 2014 evaluation and included three additional studies that were not included in the 2014 evaluation. These studies were identified in review articles, included in the evaluation by IARC (2015), or were published since the 2014 OPP evaluation. Both the 2014 and 2015 OPP evaluations considered the design and overall quality of the epidemiological studies; however, formal study quality evaluations and rankings were not conducted. In the current review, all of the studies in the 2015 report, as well as additional epidemiological articles identified from a comprehensive search and cross-referencing with available resources as described under Section 2.0, were considered in the current evaluation. The following sections provide a description of how epidemiological studies were evaluated for study quality and subsequent overall rankings, a summary of relevant studies, and a discussion of the overall results.

3.2 Considerations for Study Quality Evaluation and Scope of Assessment

This section summarizes how specific study characteristics were factored into the determination of a study's overall quality category. It should be noted that these study quality considerations are specific to the issue of concern (i.e., carcinogenic potential of glyphosate). These considerations are considered 'fit-for-purpose' under this context and could differ in another regulatory or scientific context. Although the basic concepts apply broadly, the study quality considerations are tailored specifically to studies investigating the association between glyphosate exposure and cancer outcomes. As with all research studies, the design elements of an epidemiological study have potential impacts on study quality and relevance to the research question under investigation. Each study was, therefore, judged to be of high, moderate, or low quality in each of the following six domains affecting study quality: study design, exposure assessment, outcome assessment, confounder control, statistical analysis, and susceptibility to bias (See Section 3.2.1 and Table 3.1 for general considerations under each domain). A similar approach was recently used by OPP for the evaluation of epidemiological studies for organophosphate pesticides (A. Lowit *et al.*, 2015).

Primary literature and associated meta-analyses evaluating the association between glyphosate exposure and a cancer outcome were the focus of this analysis. Reviews were only used to identify individual studies that should be considered for study evaluation. Commentaries, correspondence, and letters to the editor without original data were excluded. Of the relevant studies identified, studies with the most complete analyses utilizing the greatest number of cases and controls (e.g., pooled case-control studies) were evaluated for ranking (see Appendix B for visual representation of these studies). If studies did not collect exposure information on glyphosate from individual subjects, did not assess an outcome (e.g., biomonitoring studies), and/or did not provide a quantitative measure of an association between glyphosate and a cancer outcome, then these studies were assigned a low quality ranking and were not further evaluated in detail (see Figure 3.1). A similar process was used by JMPR for their identification of epidemiological studies for evaluating the carcinogenic potential of glyphosate and two other pesticides (JMPR, 2016).

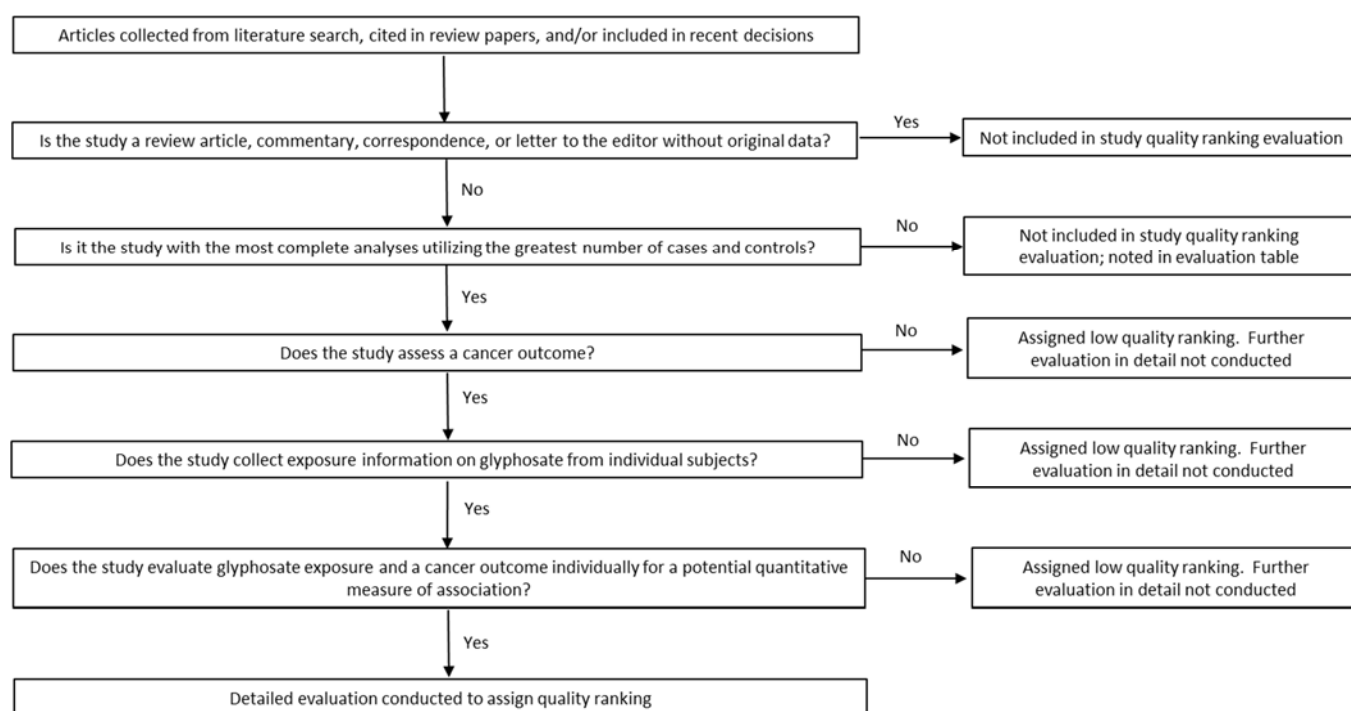


Figure 3.1. Study evaluation process for epidemiological studies.

3.2.1 Study Designs

In judging an individual study's contribution to the strength of evidence in the epidemiologic literature base, the following general hierarchy of observational study designs was considered (from most to least preferred): prospective cohort study (including nested case-control studies), case-control study, and cross-sectional study. It is important to note, however, that this hierarchy of study designs reflects the *potential* for the collection of high quality information (related to exposure, outcome, confounders, and effect modifiers) and *potential* for efficient and valid estimation of the true association. Thus, in deliberating on quality, care has been taken to

consider the circumstances and particulars of each individual study to consider whether the study was well conducted independent of the type of study design.

The study designs used in the epidemiological literature reviewed were analytical and descriptive studies. Cohort and case-control study designs are analytical studies used to evaluate relative incidence of health and disease outcomes by exposure status. Cross-sectional and ecological studies are generally considered descriptive or hypothesis-generating study designs; however, they can also be used to test hypotheses regarding prevalence of health outcomes and, under certain conditions, incidence as well.

Table 3.1. Epidemiological Study Quality Considerations^a.			
Parameter	High Score	Moderate Score	Low Score
Study Design	Cohort	Case-control	Cross-sectional/Ecological
Exposure Assessment	Questionnaire and/or interview answered by subjects for chemical-specific exposure	Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use of pesticides in general evaluated
Outcome Assessment	State or National registries, physicians, and/or special surveillance programs with cases verified by histopathological evaluation for tumors; appropriate consideration of prevalent vs. incident cases; analysis by valid method specific for biomarkers	State or National registries, physicians, and/or special surveillance programs without histopathological verification for tumors; analysis by assays that are less specific for biomarkers of interest	No outcome evaluated; unclear/no consideration for whether prevalent or incident cases are appropriate; biomarker methods not validated
Confounder Control	Good control for important confounders related to cancer, standard confounders, and known confounders for glyphosate and cancer outcomes (e.g., exposure to multiple pesticides) through study design or analytic control with well measured co-exposures (i.e., cumulative exposure)	Moderately good control for confounders related to cancer; standard variables accounted for and; attempt to control for known confounders via a less efficient measure of co-exposure (e.g., ever/never use)	No adjustments for confounders
Statistical Analyses	Appropriate to study question and design, supported by relatively adequate sample size, maximal use of data, reported well	Acceptable methods, lower/questionable study power or sample size	Minimal attention to statistical analyses, sample size evidently low, comparison not performed or described clearly

Table 3.1. Epidemiological Study Quality Considerations^a.			
Parameter	High Score	Moderate Score	Low Score
Risk of (Other) Bias	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of effect estimate, no/low potential of selection bias	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate, evidence of potential selection bias with low impact on effect estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanation for study findings, evidence of selection bias with high potential to impact effect estimate

^a Overall study quality ranking based on comprehensive assessment across the parameters.

3.2.1.1 Analytical Studies

(1) Cohort Study

In a typical cohort study, such as the AHS, individuals are classified according to exposure status (i.e., presence, absence, or magnitude of exposure) and then followed over time to quantify and compare the development (i.e., incidence) of the health outcome of interest by exposure group. Conceptually, the non-exposed comparison group in a cohort study provides an estimate of the incidence of the outcome among the exposed, had they, counter-to-fact, not been exposed. Apart from chance variations, a valid cohort study comparing exposed individuals to non-exposed individuals provides an estimate of the relative risk (or rate) of the disease associated with exposure. Ideally, the exposed and non-exposed groups are exchangeable, in the sense that switching the exposed to non-exposed, and non-exposed to exposed would yield the same measure of association (e.g., relative risk). If this were the case then, apart from chance, a cohort study would yield a measure of association equivalent to that produced in a corresponding (intervention) study where exposure status was randomly assigned.

The chief advantage of the cohort study design is that it affords the investigator the opportunity to avoid and/or adjust for potential biases (i.e., selection bias, information bias, and confounding); however, these biases may also be avoided in other well-designed study designs, such as a case-control study. Cohort studies also allow for discernment of the chronological relationship between exposure and outcome, and can be particularly efficient for studying uncommon exposures. The primary disadvantage of the cohort study design is logistical inefficiency with respect to the necessary time, expense, and other resources needed to conduct them. Cohort studies are particularly inefficient for evaluating associations with rare outcomes and diseases with long induction or latency periods. Case-control studies that are nested within a cohort study (nested case-control studies) share the attributes of the cohort study and may be more efficient. However, when follow-up throughout the study period is incomplete, the potential for selection bias is increased, especially if follow-up rates are related to exposure status.

Two sub-categories of cohort studies – prospective and retrospective – are often applied to distinguish between studies in which the health outcome has occurred (retrospective study), or has not occurred (prospective study) at the time the investigators initiate the study. This distinction is important primarily as it pertains to the potential differences in the quality (e.g.,

completeness, accuracy, and precision) of information that can be ascertained by the investigators, and also as it relates to potential sources of bias. Although not always true, the prospective study design is considered the preferable of the two, as investigators can potentially have more choices in determining how exposure, outcome, and covariate information is collected. In a retrospective study conducted to evaluate the same hypothesis, by contrast, the investigators would have to rely on exposure information based on self-reporting or historical records. Such reporting is subject to (human) errors in recall, however when such errors are uncorrelated with disease state, there can be a bias towards the null due to random exposure measurement error (information bias) and only when such errors are correlated with the disease state can there be bias away from the null.

(2) Case-Control Study

In a typical case-control study, individuals are classified according to their outcome status (i.e., cases who have developed the outcome of interest, and controls who represent the population from which the cases arise). The relative odds of exposure are then compared between cases and controls. The primary advantage of case-control studies is that they are logistically efficient relative to cohort studies, often being conducted at a fraction of the cost and in a fraction of the time as a corresponding cohort study. Case-control studies can be used to examine associations between multiple exposures and a given health outcome. They are particularly efficient for evaluating rare outcomes, but are inefficient for studying uncommon exposures. An important point to evaluate in each case-control study is the potential for selection bias, which arises if the exposure distribution among the control subjects is not representative of the exposure distribution among the population that gave rise to the cases. When participation rates between cases and controls are low or distinctly imbalanced, the potential for selection bias is increased, especially if participation rates are related to exposure status. Case-control studies that rely on self-reported exposure measures are also potentially susceptible to information bias which could result in bias towards the null or away from the null.

3.2.1.2 Descriptive Studies

Cross-sectional studies are used to evaluate associations between exposure and outcome prevalence in a population at a single point in (or period of) time. The primary advantage of a cross-sectional study is logistical efficiency. They are relatively quick and inexpensive to conduct, as a long period of follow-up is not required, and exposure and outcome assessments occur simultaneously. Cross-sectional studies have three primary *potential* disadvantages: 1) potential difficulty in discerning the temporal relationships (i.e., whether the exposure precedes the outcome); 2) estimating outcome prevalence rather than incidence of the outcome; and 3) the possible overrepresentation of cases of the outcome with long duration relative to the average in the population, and often with a better prognosis.

Ecological studies are used to evaluate associations between exposures and outcomes using population-level rather than individual-level data. The primary advantages of ecological studies are related to logistical efficiency, as they often rely on pre-existing data sources and require no individual-level exposure, outcome, or covariate assessments. The primary weakness of the ecologic study is the potential for confounding and resultant inappropriate extrapolation of associations observed on the aggregate-level to associations on an individual level. The

discrepancy that associations observed at the population level are not observed at the individual level is referred to as the ecological fallacy. Semi-ecological studies are less susceptible to the ecological fallacy due to incorporation of individual-level data on outcomes and/or confounders. The quality of these studies depends on the ability of the group exposure data to represent individual exposure and the research question of interest.

3.2.2 Exposure Measures

As described in Section 3.2 and Figure 3.1, studies assigned a low quality ranking based on an initial evaluation were not further evaluated in detail. In all of the studies included in the analysis that were reviewed and ranked for study quality, exposure information was collected from subjects and/or proxy individuals via questionnaires and/or interviews. These exposure assessments typically include questions to determine the amount of direct pesticide use or to collect information on behaviors and conditions associated with pesticide use (e.g., occupation, tasks). This type of reporting likely misclassifies actual pesticide exposure. If conducted as part of a prospective exposure assessment, these errors are likely to be non-differential with respect to the outcome(s) of interest. In a retrospective assessment, the subject or proxy has knowledge of the outcome; therefore, these errors may be differential or non-differential. Studies that exclusively used subjects rather than including proxy individuals were considered more reliable and given a higher weight given that the subjects would have a more accurate recollection of their own exposure.

3.2.3 Outcome Measures

All of the studies evaluated in detail, except one, utilized state or national cancer registries, physicians, and/or special surveillance programs to determine outcome status (i.e., subjects with or without a cancer of interest). In several studies, the cases were also verified by histopathological evaluation. Overall, outcome measures were relatively consistent across studies and these assessments are likely to have minimal errors. The remaining study evaluated in detail (Koureas et al., 2014) assessed oxidative DNA damage rather than a type of cancer. For this evaluation, the oxidation by-product 8-hydroxydeoxyguanosine (8-OHdG) was measured by enzyme immunoassay. This type of assay generally exhibits low specificity. More sensitive quantitative methods are available to analyze genomic DNA for 8-OHdG by high-performance liquid chromatography (HPLC) with electrochemical detection, gas chromatography-mass spectrometry (GC-MS), and HPLC tandem mass spectrometry. Consideration of incident or prevalent cases should also be carried out. By using only incident cases, there is greater confidence that exposures occurred prior to the development of the outcomes. Inclusion of prevalent cases can lead to an over-representation of cases with a long course of disease.

3.2.4 Confounding

The degree to which confounders were controlled varied across studies. Some studies adjusted for particular medical variables, while others did not. Some standard variables, such as age, geographical location, and sex, were either adjusted for analytically or by matching in case-control studies. Several studies collected information on potential confounders; however, not all of these variables were evaluated or results of the evaluation were not reported. The direction and magnitude for confounders are, in general, difficult to determine because they are dependent

upon the relationship of each confounding factor with glyphosate and the cancer under investigation. Several studies considered the potential for confounding from co-exposure to other pesticides; however, only a few reported effect estimates between glyphosate exposure and cancer risk adjusted for the use of other pesticides. Given most people in the epidemiological studies who use pesticides occupationally will be exposed to multiple pesticides and, in some instances, those other pesticides were observed to be risk factors for the same cancer, this is a particularly important concern to address in either the study design or in the statistical analyses. Across numerous studies, co-exposures to other pesticides was found to be positively correlated with exposure to glyphosate and exposure to those other pesticides appear to increase the risk of some cancers. As a result, the direction of confounding would be to inflate any true effect of glyphosate in the absence of statistical control. This underlines the importance of adjusting for co-exposures to other pesticides.

For NHL, other potential confounders, such as exposure to diesel exhaust fumes, solvents, ultraviolet radiation, livestock, and viruses, have been identified. Some of these are more plausible than others. For example, occupational exposure to diesel exhaust fumes (e.g., McDuffie et al., 2002; Karunanayake et al. 2008; Baris et al. 2001; Maizlish et al. 1998) and solvents (Wang et al., 2009; Kato et al., 2005; Olsson and Brandt, 1988) are considered likely to increase the risk of NHL. Agricultural workers are exposed to diesel fumes when using agricultural vehicles when applying pesticides, such as glyphosate, and when using heavy equipment during mixing, loading, and/or applying pesticides. Agricultural workers are also exposed to solvents. Solvents are often used in pesticide products to aid the delivery of the active ingredient and enhance efficacy. Solvents are also used for cleaning and maintenance/repair of agricultural equipment used for mixing, loading, and/or applying pesticides. With an association between exposure and outcome of interest, it is reasonable to consider diesel exhaust fumes and solvents as probable confounders; however, neither of these factors were accounted for in any of the studies evaluated in detail. There is also evidence that ultraviolet (UV) radiation may increase the risk of NHL (Karipidis et al., 2007; Zhang et al., 2007). As a result, there is a support that UV radiation is also a potential confounder given the extended amount of time agricultural workers spend outside performing activities, including those associated with pesticide use. Lastly, contact with farm and other animals has been investigated as a suspected risk factor for hematopoietic and lymphoid tumors (McDuffie et al., 2002). Hypothesized mechanisms to explain this association include viral transmissions, chronic antigenic stimulation, and exposure to endotoxins, fungi, and mycotoxins. None of the aforementioned potential confounders were accounted for in the studies evaluated in detail.

3.2.5 Statistical Analyses

Statistical analyses that were appropriate to the study question and study design, supported by adequate sample size, maximized the use of available data, and were well characterized in the report were weighted most highly. Acceptable statistical methods, questionable study power or sample size, and analytical choices that resulted in the loss of information were given moderate weight. Reports with only minimal attention paid to the conduct and reporting of the statistical analyses were given the lowest weight.

3.2.6 Risk of Bias

The internal validity of the studies reviewed was judged by noting the design strategies and analytic methods used in each study to constrain or eliminate selection bias, information bias, and confounding. Selection bias can occur when the sampling of the population by the investigator yields a study population that is not representative of the exposure and outcome distributions in the population sampled. Put simply, selection bias occurs if selection of the study sample yields a different estimate of the measure of association than that which would have been obtained had the entire target population been evaluated. Although there are numerous sources of selection bias, there are several mechanisms that may have induced selection bias in the studies reviewed: low participation rates of eligible individuals due to non-responsiveness or refusal (self-selection bias); loss to follow-up (i.e., failure to retain all study participants initially enrolled in the study); and, in a case-control study, control selection bias arising because the exposure distribution in the control sample does not represent the exposure distribution of the study base (i.e., the population that gave rise to the cases or more formally, the person-time experience of that population).

Information bias (also referred to as observation bias) arises when study participants are incorrectly categorized with respect to their exposure or outcome status, or when errors arise in the measurement of exposure or outcome, in the case of continuously distributed measures. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random). Non-differential misclassification of exposure (or non-differential exposure measurement error) occurs when the probability or magnitude of error in the classification or measurement of exposure is independent of the outcome status of the study participants. Non-differential exposure measurement error typically results in a bias towards the null which may obscure any true effect of the exposure of interest. Similarly, non-differential misclassification of outcome (or outcome measurement error) occurs when the probability or magnitude of error in the assignment of outcome status or level is independent of exposure status. Non-differential outcome measurement error typically does not cause bias but does decrease the precision of effect estimates and therein inflates the width of confidence intervals. In contrast, differential exposure misclassification (or measurement error) occurs when the error in the exposure assignment is not independent of the outcome status. The mechanisms that cause non-differential misclassification in the currently reviewed literature include random errors in exposure recall from subjects or proxy respondents. The mechanisms that could induce differential misclassification include recall bias and interviewer/observer bias. Note that mismeasurement of confounders can result in residual confounding of the association of interest, even when adjustment for that confounder has been conducted in the analysis.

Studies in which major sources of potential biases were not likely to be present, studies in which potential sources of bias were present, but effectively addressed and analyzed to maximize the study validity, and studies in which sources of bias were unlikely to influence the magnitude and direction of the effect estimate were given more weight than studies where sources of bias may be present, but not addressed in the study.

3.3 Review of Quality Results

Each study was judged to be of high, moderate, or low quality in each of the six domains affecting study quality, as discussed above and in Table 3.1. The results of the quality

assessment are presented separately for each group below. The quality rankings presented are specific to the current evaluation of the carcinogenic potential of glyphosate. As noted above and in Table 3.2, several studies were not included in the ranking evaluation because they did not represent the most complete analysis. Rather, the subjects were included in a larger analysis (e.g., pooled case-control study) to produce a greater number of cases and controls (see Appendix B for visual representation of these studies). For example, Cantor *et al.* (1992) was not individually evaluated for ranking because the data from this study were pooled with data from other studies in De Roos *et al.* (2003), which was included.

3.3.1 “High” Quality Group

Three studies were given a high quality ranking: De Roos *et al.* (2005), Eriksson *et al.* (2008), and Koutros *et al.* (2013).

De Roos *et al.* (2005) was a prospective cohort study that evaluated associations between various pesticide exposures, including glyphosate, and cancer incidence for numerous solid and non-solid tumors in the AHS. The aim of the AHS is to evaluate the role of agricultural exposures in the development of cancer and other diseases in the farming community. AHS recruited 52,934 licensed private pesticide applicators along with 32,345 of their spouses between 1993 and 1997. In the first two phases of the study, the cohort also included 4,916 commercial pesticide applicators from Iowa. As a prospective analysis of the AHS cohort, information was obtained from exposed subjects at enrollment and no proxies were necessary. Exposure was evaluated as ever/never use, cumulative lifetime exposure, and intensity-weighted cumulative exposure. Due to the study design, the potential for many biases were reduced. Additionally, the study adjusted and/or considered numerous factors, including use of other pesticides. Study participants provided detailed pesticide exposure information prior to enrollment in the study and this information has been incorporated into the study evaluation by determining tertile cut points and calculating effect estimates by comparing to the lowest tertile. Additional evaluations with quartiles and quintiles were performed for cancers with elevated effect estimates in the study and for NHL. As noted earlier in this document, an analysis of the AHS cohort was recently published (Andreotti *et al.*, 2017) and the findings were considered as part of this evaluation.

Eriksson *et al.* (2008) was a population-based case-control study that recruited a consecutive series of incident cases of NHL in several regions of Sweden from physicians treating lymphoma within specified health service areas. Cases were verified pathologically and matched to randomly selected controls from the national population registry by age, sex and health service area. Exposure information was collected from exposed individuals (i.e., no use of proxy respondents) using a comprehensive questionnaire including a total work history with in depth questions about exposures to pesticides, solvents, and other chemicals. Interviewers were blinded to case/control status. The study only reported minimal demographic information on subjects (age and sex) and a table with subject characteristics (e.g., smoking status, alcohol intake, physical activity, education) that could potentially be used to adjust effect estimates was not provided. Glyphosate exposure was reported in 29 cases and 18 controls during the study period. Multivariate analyses were adjusted for co-exposure to different agents, including MCPA, “2,4,5-Y and/or 2,4-D”, mercurial seed dressing, arsenic, creosote, and tar. An analysis for a potential exposure-response relationship was also conducted; however, it was not clear

whether this analysis adjusted for co-exposure to other pesticides based on the statistical methods description. The number of cases and controls were also not reported for this analysis.

Koutros *et al.* (2013) was a prospective cohort study within the AHS that evaluated the association between pesticide use and prostate cancer. Exposure information was collected from exposed subjects (no proxies necessary) through the enrollment questionnaires, as well as in a follow-up questionnaire administered 5 years after enrollment. This study evaluated the association between glyphosate and prostate cancer diagnoses from enrollment (1993-1997) through 2007 resulting in a longer follow-up time than many of the other case-control studies that utilized AHS subjects. The study used lifetime cumulative exposure and intensity-weighted cumulative exposure metrics. Analyses were also conducted using unlagged exposure and 15-year lagged exposure, which excluded the most recent 15 years of exposure for both exposure metrics. Although the effect estimate reported for glyphosate in this study was not adjusted for co-exposure to other pesticides, additional analyses were not considered necessary since there was no association observed.

3.3.2 “Moderate” Quality Group

Twenty-one case-control studies were assigned a moderate quality rating (Table 3.2). In general, these studies share many study design characteristics. Exposure information was collected from subjects and/or proxy individuals, the outcome measurement(s) utilized state/national registries and surveillance programs, appropriate statistical analyses were performed, some covariates but maybe not all relevant covariates were evaluated and/or considered, and risks of bias were minimized to some extent. Sample sizes varied across studies. Case-control studies investigating solid tumors included study populations in the United States and Canada. For non-solid tumors, study populations were located in the United States, Canada, Sweden, France, Germany, Italy, Ireland, Spain, and the Czech Republic. Although several nested case-control studies shared most of the characteristics of the AHS cohort study, these studies were primarily given a moderate quality ranking since co-exposure to other pesticides was not accounted for in the analyses.

3.3.3 “Low” Quality Group

Seven case-control and 27 cross-sectional/ecological studies were assigned a low quality ranking. All of these studies, except one case-control study (Cocco *et al.*, 2013) and one descriptive study (Koureas *et al.*, 2014), were not subjected to a detailed evaluation because they did not report a quantitative measure of an association between glyphosate exposure and a cancer outcome, did not collect information on glyphosate exposure from all subjects, and/or did not evaluate risk to a cancer outcome (Appendix D). In many instances, effect estimates were reported only for total pesticide exposure. Additionally, exposure was assumed and glyphosate-specific exposure information was not collected. In other studies, the aim of the study was to assess exposure methods for epidemiological studies and/or to evaluate the impact of exposure misclassification; therefore, there was no evaluation of a cancer outcome.

It should be noted that some of the studies assigned a low quality ranking in the current evaluation were included in the recent evaluation by IARC. There were a number of descriptive studies that evaluated the genotoxicity in human populations; however, these studies did not

meet the criteria for inclusion in the ranking as described in Section 3.2 and Figure 3.1. In most instances, these studies reported effect estimates for total pesticide exposure and/or assumed glyphosate exposure without collecting glyphosate-specific exposure information. For case-control studies, Cocco et al. (2013), Dennis et al. (2010) and Ruder et al. (2004) were included in the 2015 IARC evaluation, but were not considered informative in the current evaluation.

Detailed evaluations were not performed in the current evaluation for Dennis et al. (2010) and Ruder et al. (2004) because a quantitative measure of an association between glyphosate and a cancer outcome was not reported. Cocco et al. (2013) received a detailed evaluation and was assigned a low quality ranking. This case-control study, which evaluated lymphoma risk across six European countries, was not considered informative due to a combination of numerous limitations in the study. The sample size of the study was low with only four cases and two controls exposed to glyphosate. Control ascertainment was not consistent across countries, with a mix of hospital- and population-based controls used. The overall participation rate for population-based controls was found to be much lower than the overall participation rates of the cases or hospital-based controls. Lastly, the study was limited to ever/never use of glyphosate and did not adjust for confounders, in particular co-exposure to other pesticides. Although this study was included in the IARC evaluation, IARC also stated that the study had very limited power to assess the effects of glyphosate on risk of NHL.

The other study subjected to a detailed evaluation and assigned a low quality ranking was Koureas *et al.* (2014). This cross-sectional study evaluated the association between glyphosate exposure and oxidative DNA damage in 80 Greek pesticide sprayers. Although the study reported a non-statistically significant effect estimate for glyphosate, it is limited in its ability to contribute to the overall evaluation of the carcinogenic potential of glyphosate. The effect estimate was not adjusted for any standard covariates or potential confounders, including co-exposure to other pesticides. The sample size of the study was questionable. There were 80 subjects, but the number exposed to glyphosate was not reported. The outcome is measured using an immunoassay that is less specific for measuring the biomarker of interest than other available analytical methods. Lastly, the study evaluates primary DNA damage, but does not measure the consequence of genetic damage. An increase in oxidative DNA damage may lead to cell death or initiate DNA repair rather than lead to a mutation.

Due to the limitations in the studies assigned a low quality ranking, they do not provide reliable information to evaluate associations between glyphosate exposure and cancer outcomes. Therefore, the remaining sections of this document do not further discuss these studies except to note when a study is included in meta-analyses.

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
Alavanja <i>et al.</i> (2003)	This study was not included in the study quality ranking because the data were used in the updated analysis by Koutros <i>et al.</i> (2013).						
Andreotti <i>et al.</i> (2009)	Nested Case-control	Questionnaire answered by subjects at study enrollment followed by take-home questionnaire; examined exposure for glyphosate as ever/never, and intensity-weighted cumulative exposure days; spouses either self-administered questionnaire (81%) or telephone interview (19%)	State cancer registries without histopathological verification; exclusion of subjects with prevalent cancer at enrollment; follow-up ~ 9 years	Adjusted for age, smoking, and diabetes for both exposure metrics as well as applicator type forever/never exposure metric No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI	Exposure misclassification particularly for spouses, low response rate to take-home questionnaire (40%) but unclear if affected cases and controls differently, insufficient power for pesticide exposure interactions	Moderate
Band <i>et al.</i> (2011)	Population-based case-control Males only	Self-administered questionnaire answered by subjects or proxies for deceased subjects requesting work history and demographic information; use of a job exposure matrix to estimate exposure to pesticides	Cancer registry with histopathological verification; excluded farmers that worked all outside of British Columbia; included prostate cancer cases prior to the PSA era	Adjustment for alcohol consumption, cigarette years, education level, pipe years, and respondent type. Marital status and ethnicity not significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain ORs and 95% CIs	Recall bias, use of proxy for deceased, exposure misclassification, participation rates cited from another study, use of cancer patients as controls (excluding lung and unknown cancer)	Moderate
Brown <i>et al.</i> (1990)	Pooled population-based case-control Males only	In-person interviews using standardized questionnaire with subjects or proxies for deceased/incapacitated; supplementary questionnaire administered by telephone for Iowa subjects to obtain more	State cancer registry (Iowa) and special surveillance network including hospitals and pathology laboratories (Minnesota); cases ascertained retrospectively and prospectively (2 years after start of study);	Adjusted for vital status, age, state, ever used tobacco daily, close relative with lymphopoietic cancer, nonfarming job related to risk of leukemia in the study, exposure to substances related to risk in this study	Unconditional logistic models to obtain OR and 95% CI; questionable sample size (15 cases)	Recall bias; exposure misclassification, use of proxy respondents	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
		detailed information from those indicating pesticide use	~26% of cases deceased or too ill when identified and ~15% deceased or too ill at time of interview; histopathological verification by pathologists	(benzene, naphthalene, hair dyes) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Brown <i>et al.</i> (1993)	Population-based case-control Males only	In person interviews with standardized questionnaire to obtain detailed information on farm activities and use of pesticides from subjects or proxies	State cancer registry (Iowa) ascertained retrospectively and prospectively (2 years after start of study); ~26% of cases deceased or too ill when identified and ~15% deceased or too ill at time of interview; histopathological verification by pathologists	Adjusted for vital status and age; smoking and education evaluated and not found to be significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Logistic models to obtain OR and 95% CI; questionable sample size (11 cases)	Recall bias; exposure misclassification, use of proxy respondents	Moderate
Cantor <i>et al.</i> (1992)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by De Roos <i>et al.</i> (2003).						
Carreon <i>et al.</i> (2005)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Yiin <i>et al.</i> (2012).						
Cocco <i>et al.</i> (2013)	European multi-center case-control Hospital-based and population-based (mixed for 2 countries, only hospital-based for the rest)	Trained interviewers conducted in person interviews using structured questionnaire answered by subjects; those identified as agricultural worker on questionnaire given subsequent questions about pesticide use, crops, etc.	Surveillance centers, 20% of slides from each center reviewed by pathologist	Adjustment for age, sex, education, and center. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain ORs and 95% CIs; Low sample size (4 cases, 2 controls)	Recall bias, selection bias (low response rate for population-based controls and differed from cases), exposure misclassification, mix of hospital- and population-based controls,	Low
De Roos <i>et al.</i> (2003)	Population-based case-control Males only Pooled analysis of	Interviews with subjects or proxy for deceased subjects. Different interview techniques across states. One study collected information on	State cancer registries (one state chose a random sample, other states chose all cases), surveillance programs, and hospitals without	Adjustment for age, study site, and other pesticides. First degree relative with haematopoietic	Logistic regression and hierarchical regression to obtain ORs and 95% CIs	Recall bias, exposure misclassification, , use of proxy for deceased, , varying quality of questionnaire/interview techniques across studies	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
	Cantor <i>et al.</i> , 1992; Hoar <i>et al.</i> , 1986; Zahm <i>et al.</i> , 1990	pesticide use and then followed-up with questions on selected specific pesticides, another study had a direct question about a selected list of specific pesticides, and the last study used an open ended question without prompting for specific pesticides	histopathological verification	cancer, education, and smoking not found to be important confounders. No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
De Roos <i>et al.</i> (2005)	Prospective cohort (licensed pesticide applicators)	Questionnaire answered by subjects at enrollment and with subsequent take-home questionnaire; examined exposure as ever/never, cumulative lifetime days, and intensity-weighted cumulative exposure days	State cancer registries without histopathological verification; follow-up ~7 years	Adjustment for state of residence, age, education, smoking history, alcohol consumption, family history of cancer, use of other common pesticides No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Poisson regression to obtain RRs and 95% CIs	Major sources of potential biases unlikely, potential exposure misclassification due to any changes in exposure since enrollment, follow-up period may be limited	High
Engel <i>et al.</i> (2005)	Nested case-control Females only	Take-home questionnaire from spouses of enrolled applicators used to obtain farm exposures, general health information, and reproductive health history; Information obtained from applicators used as measure of possible indirect exposure to spouses	State cancer registries identifying malignant breast cancer; ~5 years average follow-up time	Adjusted for age, race and state. Evaluated BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause, family history of breast cancer, physical activity, smoking, alcohol consumption, fruit and vegetable consumption and education but none	Poisson regression to obtain RRs and 95% CIs	Exposure misclassification, exposure to other pesticides (however no association observed), lack of information on length of marriage could result in overestimating exposure based on husband	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
				found to be significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Eriksson <i>et al.</i> (2008)	Population-based case-control	Questionnaire answered by subjects; follow-up by phone if incomplete answers; excluded exposures that occurred during the same calendar year and year before diagnosis (cases) or enrollment (controls); minimal demographic information reported	Physicians treating lymphoma within specified health service areas and verified by pathologists	Adjustment for age, sex, year of diagnosis/enrollment, as well as exposure to other pesticides in multivariate analyses. Not stated what adjustments were made for other pesticides in latency analyses. No adjustment other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression and multivariate analyses to obtain ORs and 95% CIs; not clear how multivariate was performed; questionable sample size (29 cases, 18 controls); also included analysis of ≤ 10 vs. >10 years exposure	Recall bias, exposure misclassification, lack of subject demographics/ characteristics (e.g., smoking, alcohol consumption, race, etc)	High
Flower <i>et al.</i> (2004)	Nested case-control	Questionnaire answered by applicators at enrollment; spouses enrolled through a questionnaire brought home by applicator; females (applicators and spouses) were asked to complete a questionnaire on female and family health that collected information on children born during or after 1975	State cancer registry to identify childhood cancer cases (diagnosed from birth through 19 yrs of age) for children of parents enrolled; hybrid prospective/retrospective ascertainment; excluded female applicators	Child's age at parent's enrollment was included in model; parental age at child's birth, child's sex, child's birth weight, history of parental smoking, paternal history of cancer, and maternal history of miscarriage were evaluated but not found to be significant and not included in model No adjustment for co-	Logistic regression to obtain OR and 95% CI; calculated standardized incidence ratios to compare observed number of childhood cancer cases identified to the expected number; low/questionable sample size (6 parental cases, 13 maternal cases)	Exposure misclassification, lack of timing data to determine if exposure occurred prior to conception or during pregnancy, exposure to other pesticides (however no association observed and lack of power for adjustment)	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
				exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Hardell and Eriksson (1999)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Hardell <i>et al.</i> (2002).						
Hardell <i>et al.</i> (2002)	Population-based case-control Males only Pooled analysis of Hardell and Eriksson 1999 and Nordstrom <i>et al.</i> , 1998	Questionnaire answered by subjects or proxy for deceased subjects to obtain complete working history and exposure to different chemicals; follow-up with interview for clarification	Registries with histopathological verification	Adjustment for age, vital status, and county (by matching). Exposure to other pesticides in multivariate analysis. No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI (univariate and multivariate analyses). Questionable sample size (8 cases/8 controls)	Recall bias, exposure misclassification, use of proxy for deceased	Moderate
Hohenadel <i>et al.</i> (2011)	This study was not included in the study quality ranking because a more complete analysis was conducted by McDuffie <i>et al.</i> (2001).						
Kachuri <i>et al.</i> (2013) (extended analysis of Pahwa <i>et al.</i> 2012)	Population-based case-control Males only	Questionnaire answered by subjects or proxies; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 36.55% of samples	Adjustment for age, province, selected medical conditions, family history of cancer, use of proxy respondent, smoking status No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls, use of proxy respondents	Moderate
Karunanayake <i>et al.</i> (2012)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15%	Cancer registries or hospital in 6 Canadian provinces with histopathological verification for 49% of samples; difficulty recruiting control	Adjusted for age, province of residence, and significant medical history variables No adjustment for co-	Conditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
		random sample of those who did not; exposure based on lifetime exposure to glyphosate	participants for older age groups	exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)		controls, unable to evaluate Epstein-barr virus exposure	
Koureas <i>et al.</i> (2014)	Cross-sectional	Questionnaire answered by pesticide sprayers	Genomic DNA extracted from peripheral blood samples and oxidation by-product 8-hydroxydeoxyguanosine (8-OHdG) was determined by enzyme immunoassay; more specific methods (HPLC, GC-MS) are available for measurement	No adjustments. In univariate, occupational exposure, sex and alcohol consumption were statistically significant while DAP concentrations and smoking were not.	For univariate, chi-square test used to obtain RR and 95% CI; 8-OHdG levels transformed into binary variables (categorized as high and low using the 75 th percentile cut-off); unknown number of exposed and unexposed cases (questionable sample size possible given total number of subjects is only 80)	Recall bias, did not control for risk factors identified as statistically significant for univariate analysis, does not measure the consequence of genetic damage	Low
Koutros <i>et al.</i> (2013)	Prospective cohort Males only	Questionnaire answered by subjects at study enrollment; examined exposure as cumulative lifetime days and intensity-weighted cumulative exposure days	State cancer registries with histopathological verification; total and aggressive prostate cancers evaluated	Adjustment for age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Poisson regression to obtain RRs and 95% CIs; also included unlagged vs. lagged analysis	Exposure misclassification	High
Landgren <i>et al.</i> (2009)	Nested case-control ^a Males only	Questionnaire answered by subjects at enrollment in AHS cohort and subsequent take-home questionnaire to collect	Venous blood collected from antecubital vein and analyzed for MGUS; same method as used for controls group in	Adjusted for age and education level Association with other pesticides examined	Logistic regression models to obtain OR and 95% CI comparing to population-based	Exposure misclassification, control group not from geographical area (used control group with	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
		information on 50 pesticides; occupational exposures, medical histories, and lifestyle factors updated with 5-year follow-up interview; subjects with prior history of lymphoproliferative malignancy excluded	Minnesota	and not found to be significant so no adjustment performed No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	screening study in Olmsted County, Minnesota; questionable sample size (27 cases; 11 controls)	similar demographics from Minnesota)	
Lee <i>et al.</i> (2004a)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by De Roos <i>et al.</i> (2003).						
Lee <i>et al.</i> (2004b)	Population-based case-control White males and females only	Subjects or proxies were interviewed by telephone; those living/working on a farm asked for detailed history of pesticide use and farming information	State cancer registry or review of discharge diagnosis and pathology records at 14 hospitals; only newly diagnosed cases with confirmed adenocarcinoma of stomach or esophagus retained; controls randomly selected from a prior study conducted in geographical area	Adjusted for age and sex; evaluated BMI, smoking, alcohol consumption, educational level, family history of stomach or esophageal cancer, respondent type, dietary intake of particular vitamins and minerals, protein, and carbohydrates (included in model if changed value of OR by more than 10%) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI; questionable sample size (12 cases for stomach; 12 cases for esophagus)	Recall bias, exposure misclassification, use of proxy respondents, control selection	Moderate
Lee <i>et al.</i> (2005)	Population-based case-control	Questionnaire and/or interview with subject or proxy individuals to collect information on use of specific pesticides; telephone follow-up for unclear responses	Referral by hospitals or through state cancer registries with histopathological verification; controls selected from a previous study	Adjusted for age and respondent type; evaluated history of head injury, marital status, education level, alcohol consumption, medical history of diabetes mellitus,	Unconditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, large number of proxy respondents, control selection (historical control group from another cancer evaluation, differences in	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
				dietary intake of α- and β-carotene, and dietary fiber (included in model if changed value of OR by more than 10%) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)		exposure time period evaluated, needed to add younger controls, exposure information collected for different time periods for cases vs. controls)	
Lee <i>et al.</i> (2007)	Nested case-control	Questionnaire answered by subjects at enrollment in AHS cohort and subsequent take-home questionnaire to collect information on 50 pesticides	State cancer registries without histopathological verification; follow-up ~ 7 years	Adjustment for age, smoking, state, total days of pesticide application No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional multivariate logistic regression to obtain OR and 95% CI	Exposure misclassification, limited data on dietary factors, NSAID drug use and family cancer history	Moderate
McDuffie <i>et al.</i> , 2001	Population based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospital in 6 Canadian provinces with histopathological verification for 84% of samples; ascertainment of cases stopped in each province once target numbers were reached	Adjustment for age, province, and significant medical variables (including history of cancer in study participants and family history). No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, relatively low participation rates	Moderate
Nordstrom <i>et al.</i> , 1998	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Hardell <i>et al.</i> (2002).						
Orsi <i>et al.</i> , 2009	Hospital-based case-control	Data collection in 2 stages: 1) self-	Hospital catchment area with histopathological/	Adjustment for age, center, and	Unconditional logistic regression	Recall bias, exposure misclassification,	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
	Males only (occupationally exposed)	administered questionnaire on socioeconomic characteristics, family medical history, and lifelong residential and occupational histories and more specific information for each job held for at least 6 months, and 2) face-to-face interview with trained staff (blinded) using standardized questionnaire	cytological verification Controls were hospital based with no prior history of lymphoid neoplasms, excluding patients with cancer or a disease directly related to occupation, smoking or alcohol abuse (but history of any of these did not prevent selection as a control)	socioeconomic category. Education and housing not found to impact results. Flu immunization, previous history of mononucleosis, skin type, smoking, and drinking did not change results. Evaluated particular crops and animal husbandry as well. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	to obtain OR and 95% CI. Questionable sample size (12 cases/24 controls)	hospital-based controls	
Pahwa <i>et al.</i> (2011)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 30% of samples	Adjustment for age group, province of residence, and statistically significant medical history variables No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls	Moderate
Pahwa <i>et al.</i> (2012)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 36.5% of samples	Adjustment for age group, province of residence, and statistically significant medical history variables No adjustment for co-	Conditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (Other) Bias	Overall Ranking
		who did not; exposure based on lifetime exposure to glyphosate		exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Yiin <i>et al.</i> (2012)	Population-based case-control Pooled analysis of men with women analyzed in Carreon <i>et al.</i> (2005)	Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Cases referred by physicians or through state cancer registries with histopathological verification; controls matched within state, but not county of residence	Adjustment for age, education, sex, and , sex, and farm pesticide exposure (yes/no) No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain ORs and 95% CIs	Acknowledge other sources of bias. Recall bias, exposure misclassification, control selection (low number of deceased controls obtained)	Moderate

^a Mixed methods used in the Landgren *et al* (2009) study, with cross-sectional study design used to calculate prevalence rates comparing the AHS to a reference population MN. Pesticide risk estimates (including glyphosate) calculated using nested case-control approach, comparing AHS exposed/unexposed (ever/never) study participants.

3.4 Assessment of Epidemiological Studies for Relevance to Analysis

Using the criteria summarized in Section 3.2, a total of 63 individual literature studies were identified in the literature review and were judged as high, moderate, or low quality. The data from 7 of these studies were used in pooled analyses by other studies; therefore, they were not subjected to detailed evaluation. Overall, 3 studies, 19 studies, and 34 studies were assigned high, moderate, or low rankings, respectively. All of the high and moderate quality studies were considered relevant to the current evaluation. Additionally, the findings of a recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) have been considered in this evaluation, when appropriate.

The majority of the studies were case-control studies evaluating a wide-range of cancers in the United States and Canada. There were several case-control studies from Canada that utilized the same study population (Kachuri *et al.*, 2013; Karunanayake *et al.*, 2012; McDuffie *et al.*, 2001; Pahwa *et al.*, 2011; Pahwa *et al.*, 2012). In a similar fashion, numerous studies in the United States were nested case-control studies, where the AHS cohort served as the source population for selecting cases and controls (Andreotti *et al.*, 2009; Engel *et al.*, 2005; Flower *et al.*, 2004; Landgren *et al.*, 2009; Lee *et al.*, 2007). In these studies, a subset of the AHS cohort was selected based on their outcome status for a particular cancer and exposure information was used from the AHS enrollment questionnaire and/or during follow-up interviews. Nested case-control studies allow for testing of hypotheses not anticipated when the cohort was initially assembled. In the AHS prospective cohort studies (De Roos *et al.*, 2005; Koutros *et al.*, 2013; Andreotti *et al.*, 2017), exposure and demographic information were also obtained from the questionnaires at enrollment; however, subjects were enrolled prior to developing cancer outcomes of interest. Subjects were then followed from enrollment to a subsequent time point to determine if subjects developed cancer outcomes of interest. As such, all available subjects in the cohort are included in the evaluation of whether there was an association between a risk factor (e.g., glyphosate exposure) and outcome.

The moderate studies included a varying degree of control for confounding and biases across studies. As moderate studies, they encompass a combination of strengths and limitations. In particular, important factors that impacted the quality assessment for these studies included whether there was adjustment for known confounders, identification of control selection issues, sample size issues, and length of follow-up. As noted previously, most people in these epidemiological studies used pesticides occupationally and were exposed to multiple pesticides over their working lifetime. Therefore, exposure to other pesticides is a particularly important factor to adjust for and studies that made this adjustment were given more weight than those that did not. Similarly, control selection issues were noted in a few studies and were given less weighting than those without control selection issues. The issues ranged from concerns using hospital-based controls, using different population sources to ascertain controls within the same study, and appropriateness of using controls ascertained for another research question. Numerous studies were limited by small sample sizes, which results in large confidence intervals and reduces the reliability of the results to demonstrate a true association. Studies demonstrating low or questionable sample size were therefore given less weighting. Lastly, the length of follow-up time varied across studies.

3.5 Summary of Relevant Epidemiological Studies

A summary of the relevant studies evaluating the association between glyphosate exposure and cancer are discussed below. Results of the studies reporting data on glyphosate exposure and solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 3.3. Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.4. For study details, see Table 3.2 above and Appendix C.

3.5.1 Solid Tumor Cancer Studies

(1) Cancer at Multiple Sites from the AHS Cohort

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence of all cancers combined in the AHS cohort study and did not find an association [ever/never use relative risk ratio (RR) =1.0 with 95% confidence interval (CI) of 0.90–1.2) when adjusting for age, demographic and lifestyle factors, and exposure to other pesticides]. In addition, De Roos *et al.*, 2005 evaluated cancer at specific anatomical sites. Along with several nested case-control studies, no statistical evidence of an association with glyphosate was observed at any specific anatomical site (Table 3.3). Specifically, AHS researchers reported no evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (De Roos *et al.*, 2005; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005). The adjusted RR or odds ratio (OR) and 95% CI for these studies are provided in Table 3.3.

Findings from the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) with a longer follow-up period than De Roos *et al.* (2005) also did not find associations between glyphosate exposure and incidence of all cancers based on intensity-weighted lifetime days of glyphosate use. Furthermore, there was no evidence of an association between glyphosate use and cancers of the oral cavity, colon, rectum, pancreas, lung, melanoma, prostate, testes, bladder, or kidney. Although there was evidence of a significant positive association in one quartile only relative to intensity-weighted lifetime days of glyphosate exposure for pancreatic and lung cancer, there was no evidence of a significant positive association in any other quartile for either cancer type and the exposure-response trends were not statistically significant. As a result, these isolated findings were not considered suggestive of an association.

(2) Prostate Cancer

In a Canadian population-based study (Band *et al.*, 2011), researchers reported non-statistically significant elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). There was no adjustment made for exposure to other pesticides. This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. The AHS related studies (De Roos *et al.*, 2005; Koutros *et al.*, 2013; Andreotti *et al.*, 2017), reflect PSA-era cases

(i.e., cases which are typically identified at an earlier stage in the progression of the disease) and also did not identify an association with prostate cancer.

(3) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. Matching for age, sex, vital status, and region, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use by male farmers; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was a potential factor in this study.

Furthermore, there was no adjustment for co-exposure to other pesticides and issues noted with control selection.

A population-based case-control study evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Yiin *et al.*, 2012). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), Yiin *et al.* (2012) observed no statistical evidence of an association with glyphosate with effect estimates roughly equal to the null value following adjustment for age, education, sex, and use of other pesticides (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73).

(4) Stomach and Esophageal Cancer

In a population-based case-control study in eastern Nebraska, Lee *et al.* (2004b) investigated pesticide use and stomach and esophageal adenocarcinomas. There was no association observed between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4) after adjustment for age and sex. No adjustment was made for exposure to other pesticides.

(5) Soft Tissue Sarcoma

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate after adjustment for age, province of residence, and medical history variables (OR=0.90; 95% CI= 0.58–1.40); however, control selection issues were noted, including low response rate and selection from three different sources depending on the province of residence.

(6) Total Childhood Cancer

Flower *et al.* (2004), a nested case-control study in the AHS cohort, examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate (OR=0.84; 95% CI= 0.35–2.54). The models adjusted for the child's age at the time of parents' enrollment. There was no adjustment for exposure to other pesticides.

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
All Cancers Combined					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.9-1.2)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.0 (0.9-1.1) 1.0 (0.9-1.1)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.9 (0.8-1.0) 0.9 (0.8-1.1)	Age, demographic and lifestyle factors, and other pesticides ^b
Lung					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	0.9 (0.6-1.3)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.9 (0.5-1.5) 0.7 (0.4-1.2)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.1 (0.7-1.9) 0.6 (0.3-1.0)	Age, demographic and lifestyle factors, and other pesticides ^b
Oral Cavity					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.5-1.8)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.8 (0.4-1.7) 0.8 (0.4-1.7)	Age, demographic and lifestyle factors, and other pesticides ^b

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.1 (0.5-2.5) 1.0 (0.5-2.3)	Age, demographic and lifestyle factors, and other pesticides ^b
Kidney					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.6 (0.7-3.8)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.6 (0.3-1.4) 0.7 (0.3-1.6)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.3 (0.1-0.7) 0.5 (0.2-1.0)	Age, demographic and lifestyle factors, and other pesticides ^b
Bladder					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.5 (0.7-3.2)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.0 (0.5-1.9) 1.2 (0.6-2.2)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.5 (0.2-1.3) 0.8 (0.3-1.8)	Age, demographic and lifestyle factors, and other pesticides ^b

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
Melanoma					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.6 (0.8-3.0)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.2 (0.7-2.3) 0.9 (0.5-1.8)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.6 (0.3-1.1) 0.7 (0.3-1.2)	Age, demographic and lifestyle factors, and other pesticides ^b
Colon					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.4 (0.8-2.2)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.4 (0.9-2.4) 0.9 (0.4-1.7)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.8 (0.5-1.5) 1.4 (0.8-2.5)	Age, demographic and lifestyle factors, and other pesticides ^b
Lee <i>et al.</i> (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.0 (0.7-1.5)	Age, smoking, state, total days of pesticide application
Rectum					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.3 (0.7-2.3)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.3 (0.7-2.5) 1.1 (0.6-2.3)	Age, demographic and lifestyle factors, and other pesticides ^b

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.0 (0.5-2.0) 0.9 (0.5-1.9)	Age, demographic and lifestyle factors, and other pesticides ^b
Lee <i>et al.</i> (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.6 (0.9-2.9)	Age, smoking, state, total days of pesticide application
Colorectal					
Lee <i>et al.</i> (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.2 (0.9-1.6)	Age, smoking, state, total days of pesticide application
Pancreas					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	0.7 (0.3-2.0)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.6 (0.6-4.1) 1.3 (0.5-3.6)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 2.5 (1.0-6.3) 0.5 (0.1-1.9)	Age, demographic and lifestyle factors, and other pesticides ^b
Andreotti <i>et al.</i> (2009)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.1 (0.6-1.7)	Age group, cigarette smoking, diabetes, and applicator type
			Intensity-Weighted Exposure Days (by control median): ≤184 ≥185	1.4 (0.9-3.8) 0.5 (0.2-1.3)	Age group, cigarette smoking, and diabetes
Prostate					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.9 (0.7-1.1) 1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides ^b

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.0 (0.8-1.2) 1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides ^b
Koutros <i>et al.</i> (2013) ^c	Prospective cohort	USA: Iowa and North Carolina	Intensity-Weighted Cumulative Exposure Days (by quartile): Q1 Q2 Q3 Q4	Total prostate cancer: 0.91 (0.79-1.06) 0.96 (0.83-1.12) 1.01 (0.87-1.17) 0.99 (0.86-1.15)	Age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter
			Intensity-Weighted Cumulative Exposure Days (by quartile): Q1 Q2 Q3 Q4	Aggressive prostate cancer: 0.93 (0.74-1.16) 0.91 (0.73-1.13) 1.01 (0.82-1.25) 0.94 (0.75-1.18)	Age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter
Band <i>et al.</i> (2011)	Case-Control	Canada: British Columbia	Ever/never	1.36 (0.83-2.25)	Alcohol consumption, cigarette years, education level, pipe years, and respondent type
<i>Esophagus</i>					
Lee <i>et al.</i> (2004b)	Case-Control	USA: Nebraska	Ever/never	0.7 (0.3-1.4)	Age and sex
<i>Stomach</i>					
Lee <i>et al.</i> (2004b)	Case-Control	USA: Nebraska	Ever/never	0.8 (0.4-1.5)	Age and sex
<i>Breast</i>					
Engel <i>et al.</i> (2005)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	Wives who apply pesticides: 0.9 (0.7-1.1) Wives who never used pesticides: 1.3 (0.8-1.9)	Age, race, and state of residence
<i>Soft Tissue Sarcoma</i>					
Pahwa <i>et al.</i> (2011)	Case-Control	Canada	Ever/never	0.90 (0.58-1.40)	Age group, province of residence, and statistically significant medical history variables

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
<i>Brain (glioma)</i>					
Lee <i>et al.</i> (2005)	Case-Control	USA: Nebraska	Ever/never	Overall: 1.5 (0.7-3.1) Self-reported: 0.4 (0.1-1.6) Proxy respondents: 3.1 (1.2-8.2)	Age for overall analysis; age and respondent type for other analyses
Yiin <i>et al.</i> (2012)	Case-Control	USA: Iowa, Michigan, Minnesota, and Wisconsin	Ever/never	House/garden use: 0.98 (0.67-1.43) Non-farm jobs: 0.83 (0.39-1.73)	Age, education, sex, and use of other pesticides
<i>Total Childhood</i>					
Flower <i>et al.</i> (2004)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	Maternal use: 0.61 (0.32-1.16) Paternal use: 0.84 (0.35-2.34)	Child's age at enrollment

^a Some studies report multiple quantitative risk measurements. This table reports the most highly adjusted quantitative measurements.

^b De Roos *et al.* (2005) excluded subjects missing covariate data for demographic and lifestyle factors and exposure to other pesticides; therefore, the number of subjects included in each analysis varies.

^c Effect estimates for glyphosate reported in the supplemental web material for Koutros *et al.* (2013).

3.5.2 Non-Solid Tumor Cancer Studies

(1) Leukemia

De Roos *et al.* (2005) reported no association between leukemia and glyphosate-exposed (ever/never used) pesticide applicators in the AHS cohort. For applicators with the full data set (54,315), the RR was 1.1 (95% CI=0.6–2.4) with only adjustment for age. In the fully adjusted model, the RR was similar (RR=1.0; 95% CI=0.5–1.9). The number of participants included in the adjusted analysis was lower (n=40,716) due to the exclusion of subjects with missing covariate data. Effect estimates using cumulative lifetime exposure and intensity-weighted cumulative exposure were also found to be non-statistically significant and did not demonstrate a trend with increasing exposure. In the recently published analysis of the AHS cohort with a longer follow-up period (Andreotti *et al.*, 2017), there was no association reported between chronic lymphocytic leukemia/small lymphocytic lymphoma and chronic myeloid leukemia. For acute myeloid leukemia, an elevated but non-statistically significant association was reported in only one quartile relative to glyphosate exposure; however, there was a low number of observed cases in each of the quartiles and the overall trend was not significant. There are no other studies available evaluating acute myeloid leukemia. Given the limitations of the acute myeloid leukemia analysis, the agency will continue to follow the literature regarding the association between glyphosate exposure and risk of acute myeloid leukemia.

In a population-based case-control study in Iowa and Minnesota, Brown *et al.* (1990) did not observe an association with the ever-use of glyphosate (OR=0.9; 95% CI=0.5–1.6). A limitation in the study was the low number of cases exposed to glyphosate (n=15). Adjustments were made for several covariates, including vital status, age, tobacco use, family history of lymphopoietic cancer, high risk occupations, and high risk exposures; however, no adjustment was made for exposure to other pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and leukemia using 3 studies (De Roos *et al.*, 2005; Brown *et al.*, 1990; and Kaufman *et al.*, 2009). I^2 values were reported, which represented the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. A meta-risk ratio of 1.0 (95% CI=0.6-1.5) was obtained with an I^2 value of 0.0%, indicating consistency across the data sets. It should be noted that this analysis included data from Kaufman *et al.* (2009), which is not considered in the current evaluation because it was assigned a low quality ranking because a quantitative measure of an association between glyphosate and a cancer outcome was not reported for that study.

(2) Multiple Myeloma

In a follow-up analysis of the study population from Iowa and Minnesota used in Brown *et al.* (1990), Brown *et al.* (1993) investigated whether pesticide use was related to multiple myeloma. Among men in Iowa, the authors observed a non-statistically significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6; 11 exposed cases); however, no adjustment was made for exposure to other pesticides. The authors cautioned that while the study may lend

support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on 32 multiple myeloma cases observed in the AHS cohort. For applicators with the full data set, the RR was 1.1 (95% CI=0.5–2.4) with only adjustment for age. In the fully adjusted model excluding subjects with missing covariate data, there was a non-statistically significant elevated risk following adjustment for age, demographic and lifestyle factors, and exposure to other pesticides (RR=2.6; 95% CI=0.7–9.4). The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses or may be due to a confounder or effect modifier that is prevalent among the subgroup and has not been accounted for in the analyses. When exposure data were also stratified by tertiles with the lowest tertile of exposure as the referent category, trend analyses were not statistically significant. Non-statistically significant elevated RRs of 1.9 (95% CI: 0.6-6.3) and 2.1 (95% CI: 0.6-7.0) were estimated for the highest tertile of both cumulative and intensity-weighted exposure days, respectively. The study authors did note that small sample size precluded precise estimation (n=19 for adjusted analyses). When using never exposed as the referent category, the trend analysis was again non-statistically significant, but the RRs ranged from 2.3 (95% CI: 0.6-8.9) to 4.4 (95% CI: 1.0-20.2) from the lowest tertile to the highest tertile, respectively. When stratified by quartiles, a statistically significant trend is achieved and the RR increased to 6.6 (95% CI: 1.4-30.6); however, the authors noted that the cases were sparsely distributed for these analyses. In the recently published analysis of the AHS cohort with a longer follow-up period and 88 exposed cases (Andreotti *et al.*, 2017), there was no association observed between glyphosate exposure and multiple myeloma.

Sorahan (2015)¹² re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Using Poisson regression, risk ratios were calculated without excluding subjects with missing covariate data. When adjusted for age and sex, the RR for ever-use of glyphosate was 1.12 (95% CI of 0.5–2.49). Additional adjustment for lifestyle factors and use of other pesticides did not have a large impact (RR=1.24; 95% CI=0.52–2.94). The authors concluded that the disparate findings in De Roos *et al.* (2005) could be attributed to the use of a restricted dataset that was unrepresentative.

Landgren *et al.* (2009), within the AHS study population, also investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (MGUS). MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe an association with glyphosate use and MGUS using subjects from the AHS cohort (OR=0.50; 95% CI=0.20–1.0). No adjustment was made for exposure to other pesticides.

In a population-based case-control study (Pahwa *et al.*, 2012) among men in six Canadian provinces, a non-statistically significant elevated odds of multiple myeloma was reported in relation to glyphosate use (OR=1.22; 95% CI = 0.77–1.93), based upon 32 glyphosate exposed

¹² Funded by Monsanto

multiple myeloma cases and 133 controls. There was no adjustment for exposure to other pesticides. In an extended analysis of these data, Kachuri *et al.* (2013), using the same Canadian study population, further explored multiple myeloma in relation to days per year that glyphosate was used. Adjustment for exposure to other pesticides was also not performed in this study. For ever-use, there was a slight non-statistically significant increased odds ratio (OR=1.19; 95% CI=0.76–1.87). For light users (>0 and ≤2 days/year), there was no association (OR=0.72; 95% CI = 0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-statistically significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). Similar results were obtained when proxy respondents were excluded from the analysis. The low number of cases and controls exposed to glyphosate, particularly when exposed subjects were divided into light and heavy users, was a limitation of the study. It would be expected that effect estimates would be reduced if adjustment for co-exposure to other pesticides had been performed.

In a hospital-based case-control study conducted by Orsi *et al.* (2009) in France, 56 multiple myeloma cases and 313 age- and sex-matched controls were identified. A non-statistically significant elevated risk was observed (OR=2.4; 95% CI=0.8–7.3; 5 exposed cases and 18 exposed controls). The wide CI range can primarily be attributed to the low number of exposed cases, which reduces the reliability of the results to demonstrate a true association. Additionally, the study did not adjust for exposure to multiple pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and multiple myeloma using data from the 6 studies described above (Brown *et al.*, 1993; De Roos *et al.*, 2005; Sorahan, 2015; Pahwa *et al.*, 2012; Kachuri *et al.*, 2013; Orsi *et al.*, 2009). Meta-risk ratios were obtained using data from each of the 4 independent study populations, such that if a study population was already represented in the analysis by one study, then the same population analyzed by another study would not be included (e.g., Sorahan, 2015 and De Roos *et al.*, 2005 could not be used simultaneously in a meta-analysis). The combined meta-risk ratio based on data from prioritized studies (Brown *et al.*, 1993; Kachuri *et al.*, 2013; Orsi *et al.*, 2009; and Sorahan, 2015) was 1.4 (95% CI=1.0-1.9) using random-effects and fixed-effects models and the I^2 value = 0.0% indicating consistency across data sets. There was relatively no impact on the meta-risk ratio and associated 95% CI when secondary analyses were conducted using alternative estimates for a study population (e.g., substituting the data from Sorahan, 2015 for De Roos *et al.*, 2005).

(3) Hodgkin Lymphoma

In a Canadian case-control study, Karunanayake *et al.*, (2012) evaluated Hodgkin lymphoma (HL) and observed no association with glyphosate exposure following adjustment for age, province of residence, and medical history variables (OR=0.99; 95% CI=0.62-1.56; 38 cases). No adjustment was made for exposure to other pesticides.

In a hospital-based case-control study conducted by Orsi *et al.* (2009) in France, authors identified 87 HL cases and 265 age- and sex-matched controls. There was a non-statistically significant elevated odds ratio observed (OR=1.7; 95% CI=0.6–5.0; 6 exposed cases and 15 exposed controls). The wide CI range can primarily be attributed to the low number of exposed cases. Also, as noted earlier, this study did not adjust for exposure to multiple pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and HL using data from both of these studies. A meta-risk ratio of 1.1 (95% CI=0.7-1.6) was obtained with a I^2 value of 0.0%, indicating consistency across the data sets.

HL was also evaluated in the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) and no association was observed with glyphosate use; however, the number of cases available for this analysis was limited.

(4) Non-Hodgkin Lymphoma

NHL has about 60 subtypes classified by the WHO, which may have etiological differences (Morton *et al.*, 2014). There are analyses available for particular subtypes of NHL; however, these are particularly limited by the small sample sizes. As a result, this evaluation only presents results for total NHL with the exception of the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) where sample sizes were not limited for all subtypes.

There were six studies available that investigated the association between glyphosate exposure and NHL, which was the most for any type of cancer. As discussed in Section 3.4, these studies encompass a combination of strengths and limitations. These studies are therefore discussed in more detail in this section as compared to discussions of other cancer types in order to highlight the strengths and identify the limitations for each study.

De Roos *et al.* (2005) was the only prospective cohort study available; therefore, subjects were enrolled prior to developing cancer outcomes. Disease status was determined through state cancer registries. Exposure information was obtained from a large number of licensed pesticide applicators and no proxies were used. Exposure was evaluated as ever/never use, cumulative lifetime exposure, and intensity-weighted cumulative exposure. Due to the study design, the potential for many biases were reduced. Additionally, the study adjusted and/or considered numerous factors, including use of other pesticides. Median follow-up time was approximately 7 years.; however, as discussed in Section 3.3.1, 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. For applicators with the full data set, the RR for ever/never use was 1.2 (95% CI=0.7–1.9; 92 cases) with only adjustment for age. In the fully adjusted model excluding subjects with missing covariate data, the RR was similar following adjustment for age, demographic and lifestyle factors, and exposure to other pesticides (RR=1.1; 95% CI=0.7-1.9). Effect estimates obtained using cumulative lifetime exposure and intensity-weighted cumulative exposure were below 1 (RR = 0.6-0.9 when comparing to the lowest tertile). The recently published analysis of the AHS cohort with a longer follow-up

period of approximately 17.5 years (Andreotti *et al.*, 2017) also reported no association between glyphosate exposure and NHL overall or any of its subtypes.

De Roos *et al.* (2003) used pooled data from three case-controls studies evaluating NHL in white males from Nebraska, Kansas, and in Iowa and Minnesota (Cantor *et al.*, 1992; Hoar *et al.*, 1986; Zahm *et al.*, 1990; Appendix B). Exposure information was obtained from exposed individuals or their next of kin (i.e., proxy respondents) if the subjects were dead or incapacitated; however, techniques varied across the three studies. There is potential for selection bias due to exclusion of observations with missing covariate data, but only if the lack of the covariate data was associated with glyphosate exposure. The effect estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses adjusting for co-exposure to other pesticides. However, utilizing alternative hierarchical regression techniques to adjust for co-exposure to other pesticide exposures, the odds ratio was still elevated, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8).

Eriksson *et al.* (2008) is a Swedish case-control study that used detailed exposure information from exposed individuals (i.e., no use of proxy respondents), but only minimal demographic information was provided on subjects (age and sex) and a table with subject characteristics (e.g., smoking status, alcohol intake, physical activity, education) was not provided. Cases were identified through physicians and verified histopathologically. Glyphosate exposure, which was reported in 29 cases and 18 controls between 1999 and 2003, produced a statistically significant increased OR in the univariate analysis (OR=2.02; 95% CI=1.10–3.71); however, in the multivariate analysis adjustments were conducted for co-exposure to different agents including MCPA, “2,4,5-Y and/or 2,4-D”, mercurial seed dressing, arsenic, creosote, and tar and the OR reduced to 1.51 (95% CI=0.77–2.94) and was not statistically significant. Additional analyses were conducted to investigate the impact of various exposure times. When exposure was for more than 10 cumulative days (the median number of days among exposed controls), the OR was 2.36 (95% CI=1.04–5.37; 17 exposed cases) and for exposure less than 10 cumulative days, the OR was 1.69 (95% CI=0.7–4.07; 12 exposed cases). By dividing the exposed cases and controls using this exposure metric, wider CIs were observed due to smaller sample sizes, which reduces the reliability of the results to demonstrate a true association. Additionally, these analyses did not account for co-exposure to other pesticides. Similarly, wider CIs were also observed when exposed cases and controls were divided by a longer exposure metric. ORs of 1.11 (95% CI=0.24–5.08) and 2.26 (95% CI=1.16–4.40) were obtained for 1–10 years and >10 years, respectively. It was not clear whether this analysis adjusted for co-exposure to other pesticides based on the statistical methods description and the subjects for each exposure group were not reported. This finding, while limited to a single study, suggests that cohort studies without sufficient follow-up time or other case-control studies which did not stratify by time since first exposure may be less sensitive in detecting risk.

Hardell *et al.* (2002) used pooled data from two case-control studies in Sweden (Hardell and Eriksson, 1999; Nordstrom *et al.*, 1998; Appendix B) that examined hairy cell leukemia, a subtype of NHL, and NHL (not including hairy cell leukemia). Exposure information was collected from individuals or proxy respondents based on a working history with specific questions on exposures to different chemicals. Cases were identified from regional cancer

registries and verified histopathologically. In the univariate analysis, risk of NHL associated with glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52), but when study site, vital status, and co-exposure to other pesticides were considered in the multivariate analysis, the OR noticeably attenuated and was found to be non-statistically significant (OR=1.85; 95% CI=0.55–6.20). The wide range of the CI resulting from the small sample size (only 8 glyphosate-exposed cases and 8 glyphosate-controls).

McDuffie *et al.* (2001) is a multicenter population-based study among men of six Canadian provinces. This case-control study utilized a well-conducted exposure assessment and cases were ascertained from cancer registries or hospitals in six provinces with histopathological verification for 84% of the samples. There are concerns with control selection. There was low control participation (48%) and different sources were used for selecting controls depending on the province of residence. Effect estimates were obtained using a considerable number of exposed cases and controls (51 cases and 133 controls); however, the study did not assess co-exposure to other pesticides. There was a non-statistically significant increased risk of NHL from glyphosate exposure when adjusting for age and province (OR=1.26; 95% CI=0.87–1.80) and when adjusting for age, province and medical variables (OR=1.20; 95% CI=0.83–1.74). Medical variables found to be statistically significant included history of measles, mumps, previous cancer, skin-prick allergy tests, allergy desensitization shots, and a positive family history of cancer in a first-degree relative. It would be expected that effect estimates would attenuate if adjustment for co-exposure to other pesticides had been performed. Additional analyses were conducted to investigate differences in exposure time. When exposure was for more than 2 days/year, the OR was 2.12 (95% CI=1.20–3.73; 23 exposed cases and 36 exposed controls) compared to unexposed subjects and for exposure more than 0 and ≤ 2 days/year, the OR was 1.00 (95% CI=0.63–1.57; 28 exposed cases and 97 exposed controls) compared to unexposed subjects.

Orsi *et al.* (2009) is a French hospital-based case-control study that obtained exposure information from subjects (no proxies used) using a detailed questionnaire with lifelong residential and occupational histories followed by a discussion with a trained interviewer who was blinded to case status. No issues regarding exposure or outcome assessment were identified; however, there is potential for selection bias given the study utilized hospital-based controls (primarily from orthopedic and rheumatological departments) that may not be representative of the general population that gave rise to the cases. The study evaluated several potential confounders; however, it did not assess co-exposure to other pesticides. There was no association observed between NHL and glyphosate use (OR=1.0; 95% CI=0.5–2.2; 12 exposed cases and 24 exposed controls). The low number of cases and controls exposed to glyphosate and lack of adjustment for exposure to multiple pesticides were limitations of the study.

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; De Roos *et al.*, 2003; De Roos *et al.*, 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Since the authors identified a variety of sources of heterogeneity between publications, they decided a priori to calculate meta-risk ratio estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. I^2 values were reported as a measure of inconsistency in results. For glyphosate, the meta-risk ratio was 1.5

with a 95% CI of 1.1–2.0 and the I^2 value was 32.7% indicating relatively low levels of heterogeneity among these studies. This study combined multiple smaller studies that on their own had limitations, including small sample sizes.

The 2015 IARC evaluation noted that fully adjusted effect estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, the IARC Working Group conducted a reexamination of the results of these studies (IARC 2015). For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65, $I^2=0\%$; $p=0.589$ for heterogeneity).

Chang and Delzell (2016) conducted their own meta-analysis exploring glyphosate exposure and NHL using six independent studies (De Roos *et al.*, 2003; De Roos *et al.*, 2005; Eriksson *et al.*, 2008; Hardell *et al.*, 2002; McDuffie *et al.*, 2001; and Orsi *et al.*, 2009). A meta-risk ratio of 1.3 (95% CI=1.0-1.6) was obtained with an I^2 value of 0.0%. In a secondary analysis, the De Roos *et al.* (2003) OR using hierarchical regression was replaced by the logistic regression OR. This change had no impact on the meta-risk ratio and associated confidence interval (meta-risk ratio=1.3; 95% CI=1.0-1.6). In another secondary analysis, the OR from McDuffie *et al.* (2001) was replaced by the OR from Hohenadel *et al.* (2011), which evaluated the same study population (minus four previously misclassified NHL cases). This analysis also yielded similar results (meta-risk ratio=1.3; 95% CI=1.0-1.7). A final analysis was performed with the replacements for both secondary analyses [i.e., logistic regression OR from De Roos *et al.* (2003) and OR from Hohenadel *et al.* (2011)]. The results were relatively the same as the other meta-analyses (meta-risk ratio=1.4; 95% CI=1.0-1.8). Chang and Delzell (2016) also tested for publication bias using Egger's linear regression approach to evaluating funnel plot asymmetry, and found no significant asymmetry indicating little evidence of publication bias; however, given the small sample size ($n=6$), this analysis would lack power and the results are not considered meaningful.

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
<i>Leukemia</i>					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.5-1.9)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.9 (0.8-4.5) 1.0 (0.4-2.9)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.9 (0.8-4.7) 0.7 (0.2-2.1)	Age, demographic and lifestyle factors, and other pesticides ^b
Brown <i>et al.</i> (1990)	Case-Control	USA: Iowa and Minnesota	Ever/never	0.9 (0.5-1.6)	Vital status, age, tobacco use, family history of lymphopoietic cancer, high occupations, and high risk exposures
<i>Multiple Myeloma</i>					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	2.6 (0.7-9.4)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.1 (0.4-3.5) 1.9 (0.6-6.3)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.2 (0.4-3.8) 2.1 (0.6-7.0)	Age, demographic and lifestyle factors, and other pesticides ^b
Brown <i>et al.</i> (1993)	Case-Control	USA: Iowa	Ever/never	1.7 (0.8-3.6)	Age and vital status
Kachuri <i>et al.</i> (2013) (extended analysis of Pahwa 2012)	Case-Control	Canada	Ever/never	1.19 (0.76-1.87)	Age, province of residence, smoking status, selected medical conditions, family history of cancer, and use of a proxy respondent
			Days per year of use: 0 to ≤2 days/year >2 days/year	0.72 (0.39-1.32) 2.04 (0.98-4.23)	Age, province of residence, smoking status, selected medical conditions, family history of cancer, and use of a proxy respondent
Pahwa <i>et al.</i> (2012)	Case-Control	Canada	Ever/never	1.22 (0.77-1.93)	Age group, province of residence, and statistically significant medical history variables

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
Orsi <i>et al.</i> (2009)	Case-Control	France	Ever/never	2.4 (0.8-7.3)	Age, centre, and socioeconomic category
Sorahan (2015)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.12 (0.5-2.49)	Age and sex
Reanalysis of De Roos <i>et al.</i> (2005)				1.24 (0.52-2.94)	Age sex, lifestyle factors, and other pesticides
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren <i>et al.</i> (2009)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	0.5 (0.2-1.0)	Age and education
Hodgkin Lymphoma (HL)					
Karunanayake <i>et al.</i> (2012)	Case-Control	Canada	Ever/never	0.99 (0.62-1.56)	Age group, province of residence, and statistically significant medical history variables
Orsi <i>et al.</i> (2009)	Case-Control	France	Ever/never	1.7 (0.6-5.0)	Age, centre, and socioeconomic category
Non-Hodgkin Lymphoma (NHL)					
De Roos <i>et al.</i> (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.1 (0.7-1.9)	Age, demographic and lifestyle factors, and other pesticides ^b
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.7 (0.4-1.4) 0.9 (0.5-1.6)	Age, demographic and lifestyle factors, and other pesticides ^b
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.6 (0.3-1.1) 0.8 (0.5-1.4)	Age, demographic and lifestyle factors, and other pesticides ^b
De Roos <i>et al.</i> (2003)	Case-Control	USA: Iowa, Nebraska, Minnesota, and Kansas	Ever/never	1.6 (0.9-2.8)	Age, study site, and use of other pesticides
Eriksson <i>et al.</i> (2008)	Case-Control	Sweden	Ever/never	Multivariate: 1.51 (0.77-2.94)	Age, sex, year of diagnosis or enrollment, and exposure to other pesticides
			Days per year of use: ≤ 10 days >10 days	1.69 (0.70-4.07) 2.36 (1.04-5.37)	Age, sex, and year of diagnosis or enrollment
			Years of use: 1-10 years >10 years	1.11 (0.24-5.08) 2.26 (1.16-4.40)	Unknown

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.					
Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI) ^a	Covariate Adjustments in Analyses
Hardell <i>et al.</i> (2002)	Case-Control	Sweden	Ever/never	Multivariate: 1.85 (0.55-6.20)	Study, study area, vital status, and exposure to other pesticides
McDuffie <i>et al.</i> (2001)	Case-Control	Canada	Ever/never	1.20 (0.83-1.74)	Age, province of residence, and statistically significant medical variables
			Days per year of use: >0 and ≤ 2 days >2 days	1.00 (0.63-1.57) 2.12 (1.20 -3.73)	Age and province of residence
Orsi <i>et al.</i> (2009)	Case-Control	France	Ever/never	1.0 (0.5-2.2)	Age, centre, and socioeconomic category

^a Some studies report multiple quantitative risk measurements. This table reports the most highly adjusted quantitative measurements.

^b De Roos *et al.* (2005) excluded subjects missing covariate data for demographic and lifestyle factors and exposure to other pesticides; therefore, the number of subjects included in each analysis varies.

3.6 Discussion

A total of 63 individual studies were identified in the systematic review. The data from 7 of these studies were used in pooled analyses by other studies; therefore, they were not subjected to detailed evaluation. Overall, 3 studies, 19 studies, and 34 studies were assigned high, moderate, or low rankings, respectively. All of the high and moderate quality studies were considered informative with regard to the carcinogenic potential of glyphosate. Additionally, the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) was also considered as part of this evaluation.

There was no evidence of an association between glyphosate exposure and solid tumors, leukemia, or HL. These conclusions are consistent with those recently conducted by IARC, EFSA, and JMPR who also concluded there is no evidence of an association for these tumors at this time. The data should be considered limited though with only one or two studies available for almost all of the cancer types investigated. The remainder of this discussion focuses on multiple myeloma and NHL. Study elements for the available studies and their potential to impact effect estimates are examined; however, the discussion is applicable in most cases to all of the epidemiological studies used in this evaluation.

Multiple Myeloma

Four studies were available evaluating the association between glyphosate exposure and risk of multiple myeloma in the initial evaluation presented to the SAP in December 2016 (Brown *et al.*, 1993; De Roos *et al.*, 2005; Orsi *et al.*, 2009; Pahwa *et al.*, 2012). Since that time, a recent analysis of the AHS cohort has been published (Andreotti *et al.*, 2017), which included evaluation of multiple myeloma. One reanalysis (Sorahan, 2015) and one extended analysis (Kachuri *et al.*, 2013) were also included in the evaluation. The effect estimates for ever/never use ranged from 1.19 to 2.6 although none were found to be statistically significant. Only one study (De Roos *et al.*, 2005) adjusted for co-exposures to other pesticides; therefore, potential confounding was not addressed in the other studies. There was an indication of a possible exposure-response relationship; however, this was the only study that evaluated the exposure-response relationship for multiple myeloma. Reanalysis of the full dataset by Sorahan (2015) raised concerns about whether the restricted dataset used for these analyses was representative of the whole cohort. Furthermore, in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017) with a longer follow-up period and almost 5 times more exposed cases, there was no evidence of an association between glyphosate exposure and risk of multiple myeloma. There was a single study of MGUS, a precursor to multiple myeloma, which showed decreased risk with exposure to glyphosate; however, the study did not adjust for exposure to other pesticides. Overall, the available evidence does not link glyphosate exposure to multiple myeloma.

NHL

Six studies were available evaluating the association between glyphosate exposure and risk of NHL in the initial evaluation presented to the SAP in December 2016. Since that time, a recent analysis of the AHS cohort has been published (Andreotti *et al.*, 2017), which included evaluation of NHL. Effect estimates for ever/never use ranged from 1.0-1.85 in adjusted

analyses with none reaching statistical significance (Figure 3.2). Two of these studies did not adjust for co-exposures to other pesticides (McDuffie *et al.*, 2001; Orsi *et al.*, 2009). Many of the evaluated studies were limited by small sample sizes, which resulted in large confidence intervals and reduced the reliability of the results to demonstrate a true association. Meta-analyses were performed by IARC (2015) and Chang and Delzell (2016) using these results for the ever/never use metric. Both analyses reported similar meta-risk ratios ranging from 1.3-1.5, depending on the effect estimates and studies included in the analyses. Any of the meta-analysis estimates that were statistically significant were all borderline with the lower limit of the 95% CI just slightly over 1. For example, the lower 95% confidence limit reported by IARC (2015) was 1.03 and the lower 95% confidence limit displayed in Figure 3.2 generated by the agency is 1.01. It should also be noted that publication bias may play a role in this evaluation given there is a tendency to only publish positive results and potential concerns regarding glyphosate have only been raised in recent years.

With respect to meta-analyses, caution should be taken when interpreting results. Meta-analyses are a systematic way to combine data from several studies to estimate a summary effect. Analyses were performed with 6 studies, which many would consider small for performing meta-analyses. Rarely will meta-analyses synthesize data from studies with identical study designs and methods. In the meta-analyses performed by IARC (2015) and Chang and Delzell (2016), inclusion was primarily based on whether a study addressed the broader question regarding the association between glyphosate exposure and risk of NHL. For meaningful results, careful consideration of whether studies are similar and should be combined in the analysis. Furthermore, the bias and confounding issues inherent for each individual study are carried over into the meta-analyses. Across the NHL studies, study characteristics varied, such as overall study design (i.e., cohort and case-control), source population, proxy respondent use, covariate adjustments, and confounding control. Even if these differences are not detected statistically, the meta-analysis estimate should be considered in the context of the data that are used to generate it.

Using cumulative lifetime and intensity-weighted cumulative exposure metrics, all effect estimates were less than 1 (OR = 0.6-0.9 when comparing to the lowest tertile) in the AHS cohort study (De Roos *et al.*, 2005). Similar results were obtained in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017). Two case-control studies (Eriksson *et al.*, 2008; McDuffie *et al.*, 2001) evaluated the association of glyphosate exposure and NHL stratifying exposure by days per year of use. These studies obtained effect estimates greater than 1, which conflicted with the results in the prospective cohort study; however, these estimates from the case-control studies do not appear to be adjusted for co-exposures to other pesticides. By dividing the total number of exposed cases and controls by these exposure metrics in Eriksson *et al.* (2008), wider confidence intervals were observed due to small sample sizes, which reduces the reliability of the results to demonstrate a true association. Furthermore, as mentioned previously (and will be discussed further below), there was clearly strong potential for confounding from exposure to other pesticides. In each instance where a study adjusted for co-exposure to other pesticides, the adjusted effect estimate decreased in magnitude, including other analyses performed in one of these case-control studies. Consequently, lack of adjustment for co-exposure to other pesticides in these analyses could partially explain the conflicting results between the cohort and case-control studies.

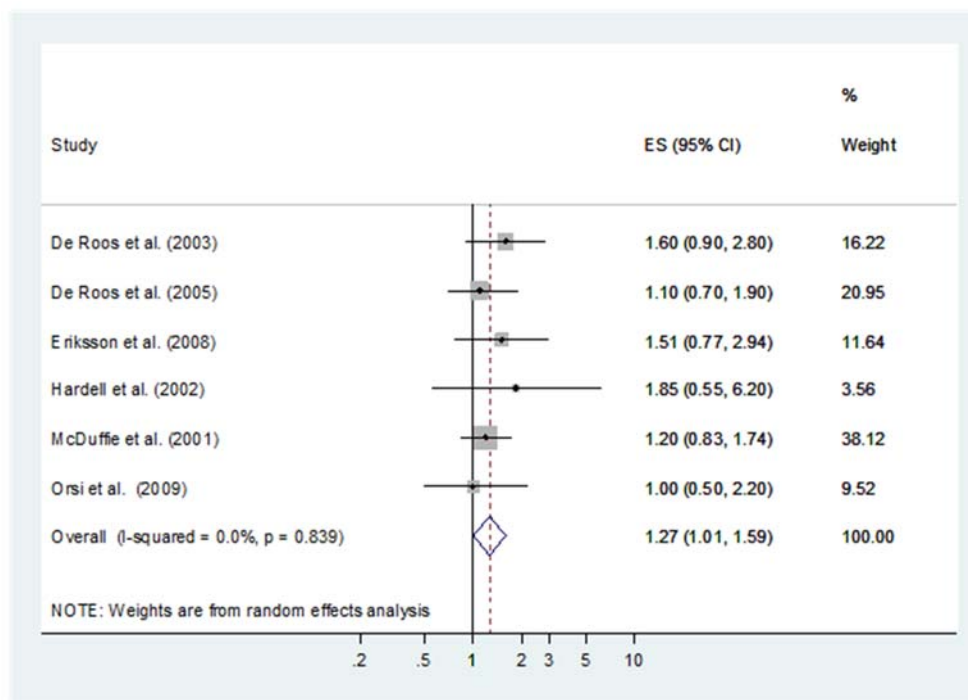


Figure 3.2. Forest plot of effect estimates (denoted as ES for effect sizes) and associated 95% confidence intervals (CI) for non-Hodgkin lymphoma (NHL).

The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Control for confounding varied considerably across studies (Table 3.2). Studies primarily adjusted for standard variables, such as age, gender, and residency location. Co-exposure to other pesticides was considered for several of the NHL studies for ever/never use (De Roos *et al.*, 2003; De Roos *et al.*, 2005; Eriksson *et al.*, 2008; Hardell *et al.*, 2002); however, analyses of exposure-response and latency effects did not appear to adjust for these co-exposures. The recent analysis by Andreotti *et al.* (2017) also adjusted for co-exposure to other pesticides.

There is clearly a strong potential for confounding by co-exposures to other pesticides since many are highly correlated and have been reported to be risk factors for NHL. In the studies that did report a quantitative measure adjusted for the use of other pesticides, the risk was always found to be closer to the null than the risk calculated prior to this adjustment. For examples, Eriksson *et al.* (2008) reported unadjusted and adjusted effect estimates of 2.02 (95% CI: 1.10-3.71) and 1.51 (95% CI: 0.77-2.94), respectively. Comparing the magnitude of those effect sizes on the natural log scale, the unadjusted effect was $\beta=0.70$ (95% CI: 0.10, 1.31) while the adjusted effect was $\beta=0.41$ (95% CI: -0.26, 1.08), suggesting a difference compatible with a degree of confounding by those herbicide co-exposures which appeared to have inflated the unadjusted effect upwards by 70% on the natural log scale (or by 46% on the OR scale). This demonstrates the profound effect this adjustment has on effect estimates and the concern for residual confounding by other pesticides that cause NHL themselves. As discussed in Section 3.2.4, other potential confounders have also been identified. With an association between glyphosate exposure and the outcome of interest, occupational exposure to diesel exhaust fumes, solvents, livestock and other farm animals, and UV radiation are highly likely confounders in the

NHL studies; however, none of the studies accounted for these potential confounders. These confounders and/or other unknown factors could explain the increased risk of NHL among farmers, particularly since increased risk of NHL to farmers has been previously documented and existed prior to the introduction of glyphosate.

Recall bias and missing data are also limitations in most of the studies. In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain discrepancies in study findings. During their lifetime, farmers are typically exposed to multiple pesticides and often several may be used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, the results can be subject to misclassification and recall bias.

Furthermore, the use of proxy respondents has the potential to increase recall bias and thus may increase exposure misclassification, especially for proxy respondents not directly involved in farming operations that may be more prone to inaccurate responses than directly interviewed subjects. In some of the NHL studies, the study participants were interviewed directly to assess exposure (De Roos *et al.*, 2005; Eriksson *et al.*, 2008; McDuffie *et al.*, 2001; Orsi *et al.*, 2009), making proxy respondent use a non-issue for these studies. In other studies, however, study participants or proxy respondents were interviewed to assess exposure (Hardell *et al.*, 2002, De Roos *et al.*, 2003). De Roos *et al.* (2003) did not find type of respondent to be statistically significant, but Hardell *et al.* (2002) did not conduct analyses to evaluate the impact of proxy use. In non-NHL studies, proxy analyses were conducted in a small subset (Kachuri *et al.*, 2013; Lee *et al.*, 2004b; Lee *et al.*, 2005; Yiin *et al.*, 2012) and differences in effect estimates were often observed. In a few studies, respondent type was used as an adjustment variable when calculating effect estimates (Band *et al.*, 2011; Kachuri *et al.*, 2013; Lee *et al.*, 2005). As with all study design elements of case-control studies, one concern is whether or not the use of proxy respondents had a differential impact on the cases and controls included in the study because any differential impact may result in differential exposure misclassification. When use of proxy respondents was comparable for cases and controls in the full study population, it could be assumed that there is less concern for potential recall bias from the use of proxy respondents. In Hardell *et al.*, (2002), the percentage of cases and controls with proxy respondents was not fully reported for cases and controls though and this adds a potential source of uncertainty for the study. Moreover, when proxy respondents were used in a study, the percentages were usually reported only for the full study population and were not reported for the specific cases and controls exposed to glyphosate. This lack of information makes it difficult to assess the degree to which recall bias may have occurred due to the use of proxy respondents.

Previously, some have argued that the follow-up period (median = 7 years) in De Roos *et al.* (2005) is not sufficiently long to account for the latency of NHL (Portier *et al.*, 2016); however, an analysis of the AHS cohort was recently published (Andreotti *et al.*, 2017) with an extended

follow-up of 17.5 years. This study reported no association between glyphosate exposure and all lymphohematopoietic cancers, NHL, or any of its subtypes across exposure metrics. No association was observed in unlagged or lagged analyses, after adjustment for pesticides linked to NHL in previous AHS analyses, and after exclusion of multiple myeloma from the NHL grouping.

It was also noted that reference groups differed across studies. For example, some studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; and Eriksson *et al.*, 2008) eliminated cases and controls who had been exposed to certain classes of pesticides, which may have resulted in selection bias and/or recall bias that may ultimately impact the effect estimates obtained in these studies. In the dose-response analysis by De Roos *et al.* (2005), the lowest exposed tertile was used as the reference group in an effort to reduce the potential for residual confounding by unmeasured covariates due to lack of comparability observed between the never exposed group and the higher exposed groups. Analyses were also performed using the unexposed group as the reference. This study consistently found no evidence of an association between glyphosate exposure and NHL using different exposure metrics and reference groups. Similarly, there was no evidence of an association observed in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017) with a longer follow-up period.

There are conflicting views on how to interpret the overall results for NHL. Some believe that the data are indicative of a potential association between glyphosate exposure and risk of NHL. This is primarily based on reported effect estimates across case-control studies and the associated meta-analyses greater than 1. Additionally, the analysis conducted by Eriksson *et al.* (2008) observed a slightly statistically significant increase for those with more than 10 years of exposure prior to diagnosis. There were also two case-control studies that investigated the association of glyphosate exposure and NHL by stratifying exposure by days per year of use that reported effect estimates greater than 1 for groups with the highest exposure.

Conversely, others have viewed the effect estimates as relatively small in magnitude and observed associations could be explained by chance and/or bias, particularly since studies have reported farmers develop NHL at excess rates and this risk existed prior to the introduction of glyphosate. All of the effect estimates for ever/never use were non-statistically significant. Several studies reported effect estimates approximately equal to the null. The widest confidence intervals were observed for the highest effect estimates indicating these effect estimate are less reliable. Sample sizes were limited in several of these case-control studies. Meta-analyses were based on studies with varying study characteristics. Given the limitations and concerns discussed above for the individual studies included in this evaluation, chance and/or bias cannot be excluded as an explanation for the relatively small increase observed in the meta-risk ratios. Meanwhile, analyses performed by De Roos *et al.* (2005) and Andreotti *et al.* (2017) reported effect estimates less than 1 for cumulative lifetime exposure and intensity-weighted cumulative exposure and these extensive analyses did not detect any exposure-response relationship, which conflicts with the two case-control studies that indicate potential for an exposure-response relationship comparing two groups stratified by days per year of use. Although increased effect estimates were observed in one case-control study (Eriksson *et al.*, 2008) for subjects exposed more than 10 years prior to diagnosis and in two case-control studies (McDuffie *et al.*, 2001; Eriksson *et al.*, 2008) that stratified exposure by days per year of use, none of these analyses

appeared to adjust for exposures to other pesticides, which has been found to be particularly important for these analyses and would be expected to attenuate these estimates towards the null. Furthermore, none of the studies in this evaluation of glyphosate exposure and risk of NHL accounted for other potential confounders, such as diesel exhaust fumes, solvents, animals, and UV radiation.

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.

4.0 Data Evaluation of Animal Carcinogenicity Studies

4.1 Introduction

Cancer bioassays in animals have historically been the primary studies available to evaluate cancer hazard in humans since, until recently, epidemiological evidence was limited. The results of these bioassays, as well as results from screening assays for genotoxicity, are considered in a weight-of-evidence approach to determine the potential of a chemical to induce cancer in humans. Carcinogenicity studies in two rodent species are required for the registration of food use pesticides or when the use of a pesticide is likely to result in repeated human exposure over a considerable portion of the human lifespan (40 CFR Part 158.500). Rodent carcinogenicity studies identified from the data collection phase of the systematic review were evaluated for study quality and acceptable studies were evaluated in the context of the 2005 EPA Guidelines for Carcinogen Risk Assessment as described in Sections 4.2 and 4.3 below, respectively. This included studies using glyphosate salts, which dissociate quickly in aqueous environments to the glyphosate acid and the corresponding cation. The cations would not be expected to impact the toxicity results compared to studies where animals are treated with glyphosate acid alone.

4.2 Consideration of Study Quality for Animal Carcinogenicity Studies

The agency has published test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200) and combined chronic/carcinogenicity studies (OCSPP 870.4300) in rodents which have been harmonized with OECD guidelines (Test Nos. 451 and 453). Test substances are typically administered in animal carcinogenicity studies by the oral route for food use pesticides. The studies are generally conducted in mice and rats with exposure durations of 18-24 months for mice and 24 months for rats, which represent exposures of the majority of the expected lifespan in these animals. Guideline carcinogenicity studies are designed to test three or more doses in both sexes (with at least 50 animals/sex/dose) with adequate dose spacing to characterize tumor dose-response relationships. Key considerations when evaluating carcinogenicity studies for cancer hazard assessment include identification of target organs of carcinogenicity, increased incidence of tumors or proportion of malignant neoplasms, and reduction in the time to appearance of tumors relative to the concurrent control group (OECD TG 451).

There are a number of criteria the agency uses when evaluating the technical adequacy of animal carcinogenicity studies. A primary criterion is the determination of the adequacy of dosing. The 2005 EPA Guidelines for Carcinogen Risk Assessment recommends that the highest dose level selected should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors; or without inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms); however, the high dose need not exceed 1,000 mg/kg/day (i.e., limit dose) (OCSPP 870.4200; OCSPP 870.4300). Additional criteria to judge the technical adequacy and acceptability of animal carcinogenicity studies are provided in the test guidelines as well as other published sources (NTP, 1984; OSTP, 1985; Chhabra *et al.*, 1990). As stated in the 2005 EPA Guidelines for Carcinogen Risk Assessment, studies that are judged to be wholly inadequate in protocol, conduct or results, should be discarded from

analysis. Studies the agency consider acceptable are further evaluated for potential tumor effects.

Following study quality evaluation, a total of 8 chronic/carcinogenicity studies in the rat and 6 carcinogenicity studies in the mouse were considered acceptable for use in the current evaluation for the active ingredient glyphosate and were subsequently evaluated in the context of the 2005 EPA Guidelines for Carcinogen Risk Assessment as described in Section 4.3. A number of studies were judged to be inadequate in protocol, conduct or reporting and were not considered in the analysis of glyphosate. These studies and the justification for not including them in the analysis are listed below:

1. A two-year chronic oral toxicity study in Albino rats by Reyna (1974)¹³. The study was considered inadequate to assess carcinogenicity due to insufficient reporting on the histopathology findings in the control and treatment groups. Approximately 70 animals were unaccounted for across the study.
2. A two-year drinking water study in Wistar rats with a formulated product (13.6% ammonium salt) by Chruscielska *et al.*, (2000). In addition to deficiencies including inadequate reporting of water consumption and body weight data, this study was conducted with a glyphosate formulated product and not the active ingredient glyphosate, which is the focus of this review. Glyphosate formulations contain various components other than glyphosate and it has been hypothesized these components are more toxic than glyphosate alone. The agency is collaborating with NTP to systematically investigate the mechanism(s) of toxicity for glyphosate and glyphosate formulations. This project is discussed in more detail in Section 7.0 of this document.
3. An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) on the skin. Study deficiencies included small number (20) of animals, tested only males, and lack of histopathological examination.
4. A carcinogenicity study in Swiss albino mice (Kumar, 2001)¹⁴. This study was not included due to the presence of a viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all dose groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are also a common cause of lymphoma in many different strains of mice (Ward, 2006). For example, Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice infected with MuLVs. Although the lymphoma incidences in Kumar (2001) were within or near normal background variation, it is not clear whether or not the viral infection may have contributed to the lymphoma incidence reported or the lower survival seen at the high dose in this study.

¹³ MRID 00062507.

¹⁴ MRID 49987403. In Greim *et al.* (2015), the same study is cited as Feinchemie Schwebda (2001).

5. A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included. The agency does not have access to this study to perform an independent assessment of its conduct and; however, Greim *et al.* (2015) stated that the study “is considered unreliable for carcinogenicity evaluation” and there were “several deviations from the OECD Test Guideline 453”.

4.3 Assessment of Animal Carcinogenicity Studies

The agency considers many factors when interpreting the results of carcinogenicity studies. The 2005 EPA Guidelines for Carcinogen Risk Assessment are intended as a guidance only and does not provide a checklist for determining whether tumor findings are related to treatment. These guidelines emphasize the importance of weighing multiple lines of evidence in reaching conclusions regarding human carcinogenic potential of chemicals. Evaluation of observed tumor findings takes into consideration both biological and statistical significance. There are several factors in the 2005 EPA Guidelines for Carcinogen Risk Assessment used in the weight-of-evidence evaluation of individual studies. For this evaluation, the interpretation of the evidence related to tumor findings is described below.

Dose Selection

Doses should be selected based on relevant toxicological information. Caution is taken in administering an excessively high dose that would confound the interpretation of the results to humans. As mentioned above, the 2005 EPA Guidelines for Carcinogen Risk Assessment recommends that the highest dose level selected should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors; or without inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms); however, the high dose is not recommended to exceed 1,000 mg/kg/day (OCSPP 870.4200; OCSPP 870.4300). Doses should provide relevant dose-response data for evaluating human hazard for human health risk assessment. In the case of glyphosate, the low (oral) systemic toxicity and limited pharmacokinetic (PK) data for this chemical make it difficult to define a maximum tolerated dose (MTD) for the cancer bioassays. A large number of the carcinogenicity studies conducted with glyphosate approach or exceed the limit dose. The 2005 EPA Guidelines for Carcinogen Risk Assessment state that “weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed”. As such, the agency puts less weight on observations of increased incidence of tumors that only occur near or above the limit dose.

Statistical analyses to evaluate dose response and tumor incidences

The main aim of statistical evaluation is to determine whether exposure to the test agent is associated with an increase in tumor development, rather than due to chance alone. Tumors were selected for statistical analyses in the current evaluation if the study report identified tumors as statistically significant and/or have been identified by the reviewer as potentially biologically significant based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls. For toxicological studies submitted to the agency for pesticide registration, including animal carcinogenicity studies, detailed reviews are performed, which summarize study findings and identify effects, such as tumors, for evaluation.

Statistical analyses should be performed on each tumor type separately. The incidence of benign and malignant lesions of the same cell type, usually within a single tissue or organ, are considered separately, but may be combined when scientifically defensible (McConnell *et al.*, 1986). 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. The 2005 Guidelines for Carcinogen Risk Assessment states that:

“A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.”

In the current evaluation, animals sacrificed for interim evaluations or died prior to the interim sacrifices were not included in the statistical evaluations to avoid dilution of a potential carcinogenic effect. Additionally, survival was evaluated across dose groups and no significant mortality differences were observed in any of the studies. As a result, there was no need to incorporate survival adjustments into the analyses (e.g., Peto prevalence test). The Cochran-Armitage Test for Trend (Snedecor and Cochran, 1967; one-sided) was used for trend analysis. For pairwise comparisons, the Fisher Exact Test (Fisher, 1950; one-sided) was used to determine if incidences observed in treated groups were different from concurrent controls. Furthermore, the 2005 EPA Guidelines for Carcinogen Risk Assessment state that “considerations of multiple comparisons should also be taken into account”. Multiple comparison methods control the familywise error rate, such that the probability of Type I error (incorrect rejection of the null hypothesis or “false positive”) for the pairwise comparisons in the family does not exceed the alpha level. In the current evaluation, the Benjamini-Hochberg correction method was used to adjust for multiple comparisons (Benjamini and Hochberg, 1995).

For the current evaluation, statistical significance observed in either test is judged in the context of all of the available evidence. Statistically significant responses may or may not be biologically significant and vice versa (Hsu and Stedeford, 2010; EPA, 2005). If a trend was found to be statistically significant, a closer examination of the tumor incidence was taken to determine whether the data demonstrate a monotonic dose-response where an increase in tumor incidence is expected with corresponding increase in dose. Therefore, statistically significant results with fluctuating tumor incidence across doses are not weighed as heavily as those displaying a monotonic dose-response. If a pair-wise comparison was found to be statistically significant, a closer examination of the tumor incidence and other lines of evidence was taken to determine whether the response was biologically significant. Factors considered in determining the biological relevance of a response are discussed below.

All statistical analyses were reanalyzed for the purposes of this evaluation to ensure consistent methods were applied (M. Perron; 12-DEC-2017; TXR#0057690).

Historical Control Data

As indicated in the 2005 EPA Guidelines for Carcinogen Risk Assessment (Section 2.2.2.1.3), the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals. Additional insight into the statistical and/or biological significance of a response can come from the consideration of historical control data (Tarone, 1982; Haseman, 1995; EPA, 2005). 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. 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.

Historical control data are also useful to determine if concurrent control tumor incidences are consistent with previously reported tumor rates (Haseman, 1995). Historical control data available to the agency from the performing laboratory for the same species and strain for a study were considered in the current evaluation. These data were primarily generated within 3 years and in limited cases within 5 years of the study date. Given the large number of age-related tumor outcomes in long-term rodent bioassays, and thus the large number of potential statistical tests run, 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. Consequently, in the current evaluation, unusually low incidence in concurrent controls was noted when applicable and considered as part of the weight-of-evidence for the tumor findings. Identification of common or uncommon situations prompts further thought about the meaning of the response in the current study in context with other observations in animal studies and with other evidence about the carcinogenic potential of the agent.

Evidence of supporting preneoplastic lesions or related non-neoplastic lesions

Carcinogenicity rodent studies are designed to examine the production of tumors as well as preneoplastic lesions and other indications of chronic toxicity that may provide evidence of treatment-related effects and insights into the way the test agent produces tumors (EPA, 2005). As such, the presence or lack of supporting preneoplastic or other related non-neoplastic changes were noted in the current evaluation of each study and considered in the weight-of-evidence to aid in the determination of biological significance since these lesions would not be expected for age-related tumors in carcinogenicity with continuous treatment. In the current evaluation, the agency investigated lesions in organs where tumors were observed and demonstrated biological significance based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls.

Additional Considerations

Other observations can strengthen or lessen the significance of tumor findings in carcinogenicity studies. Such factors include: uncommon tumor types; tumors at multiple sites; tumors in multiple species, strains, or both sexes; progression of lesions from preneoplastic to benign to malignant; reduced latency of neoplastic lesions (i.e., time to tumor); presence of metastases; unusual magnitude of tumor response; and proportion of malignant tumors (EPA, 2005). The

agency considers all of the above factors when determining the significance of tumor findings in animal carcinogenicity studies.

4.4 Summary of Animal Carcinogenicity Studies

A total of 8 chronic toxicity/carcinogenicity studies in the rat¹⁵ and 6 carcinogenicity studies in the mouse were considered acceptable and evaluated in the weight-of-evidence analysis for glyphosate. This includes all of the studies that were part of the 2015 CARC evaluation plus an additional 4 studies identified from the systematic review. In the 2015 CARC evaluation, for some of the studies considered, the CARC relied on summary data that was provided in the supplement to the Greim *et al.* (2015) review article. Due to the ongoing data collection effort and the acquiring of studies not previously submitted, the agency no longer needs to rely on the Greim *et al.* (2015) review article for the study data generated in relevant studies, allowing for a more complete and independent analysis. It should be noted that studies have been cited differently in this evaluation as compared to Greim *et al.* (2015) so these alternative citations have been noted for applicable studies.

The carcinogenicity studies conducted in the rat and mouse that were considered for the analysis are discussed in Sections 4.5 and 4.6, respectively. In these sections, short study summaries are presented which include information on the study design (including test material, strain of animal used, and doses and route of administration) as well as study findings including effects on survival, general toxicity observed, relevant non-neoplastic lesions, and the incidence and characterization of any tumor findings. The characterization of the tumor response(s) is based on the considerations previously discussed in Section 4.3 for interpreting the significance of tumor findings in animal carcinogenicity studies. The rat and mouse carcinogenicity studies are all summarized in Table 4.11 and Table 4.18, respectively.

4.5 Rat Carcinogenicity Studies with Glyphosate

4.5.1 Lankas, 1981 (MRID 00093879)¹⁶

In a chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at dietary doses of 0, 3/3, 10/11, and 31/34 mg/kg/day (M/F) for 26 months.

There were no treatment-related effects on survival at any dose level. The highest dose tested of approximately 31 mg/kg/day was not considered a maximum tolerable dose to assess the carcinogenic potential of glyphosate. Consequently, a second study (Stout and Ruecker, 1990) was conducted at higher doses, which is summarized in the Section 4.5.3.

A statistically significant trend was reported for the testicular interstitial tumors; however, closer examination of the tumor incidence indicates that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose. The

¹⁵ Note: the original draft of this Issue Paper included 9 studies in rats; however, one study (Burnett, 1979) was removed since the study was conducted with a contaminant of glyphosate, not the active ingredient glyphosate.

¹⁶ In Greim *et al.* (2015), the same study is cited as Monsanto (1981).

incidence at the high dose was found to be statistically significant as compared to the concurrent controls (raw and adjusted p-values).

**Table 4.1. Testicular Interstitial Cell Tumors in Male Sprague-Dawley Rats (Lankas, 1981)
Cochran-Armitage Trend Test & Fisher's Exact Test Results.**

	0 mg/kg/day	3.05 mg/kg/day	10.3 mg/kg/day	31.49 mg/kg/day
Incidence (%)	0/47 ^a (0)	3/49 (6)	1/47 (2)	6/50 (12)
Raw p-value =	0.011**	0.129	0.500	0.016*
Adjusted p-value =	0.032*	0.172	0.500	0.032*

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01.

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

The study report provided historical control information for 5 studies of similar duration (24-29 months) run concurrently within 9 months of the termination of the study in the same laboratory. The historical control range for this tumor type was 3.4%-6.7% (mean = 4.5%) when considering all animals. When only considering animals that survived to terminal sacrifice, the historical control range was 6.2%-27.3% (mean = 9.6%). These data indicate that the incidence of testicular cell tumors in concurrent controls (0%) appears to be unusually low for this tumor type. Furthermore, the incidence at all doses, including the high dose, was within the historical control range when evaluating animals at terminal sacrifice. There were no supporting preneoplastic or other related non-neoplastic changes observed.

4.5.2 Stout and Ruecker, 1990 (MRID 41643801)¹⁷

In a chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary doses of 0, 89/113, 362/457 or 940/1183 mg/kg/day M/F) for 24 months. The highest dose tested in this study approaches or exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Tumor findings at these high doses are given less weight.

There was no significant increase in mortality. Three types of tumors were evaluated in this study: pancreatic cell adenomas, hepatocellular adenomas, and thyroid C-cell adenomas in males. A discussion of each tumor type by organ is presented below:

1. Pancreas: Tumor incidences of pancreatic islet cell tumors in male rats are presented in Tables 4.2. The incidence of pancreatic islet cell tumors lacked monotonic dose-responses and trend analyses were not statistically significant. There was also no statistical significance of the pairwise comparisons. Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range for the adenomas was 1.8%-8.3% (mean = 5.3%). These data are presented in Table 4.3 and indicate that the incidence of adenomas in concurrent controls (2%) was at the lower limit

¹⁷ In Greim *et al.* (2015), the same study is cited as Monsanto (1990).

of the historical range. There were no supporting preneoplastic or other related non-neoplastic changes observed and no evidence of progression from adenomas to carcinomas.

Table 4.2. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990) Cochran-Armitage Trend Test & Fisher's Exact Test Results.				
Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma				
Incidence	1/43 ^a	8/45	5/49	7/48 ^b
(%)	(2)	(18)	(10)	(15)
Raw p-value =	0.176	0.018*	0.135	0.042*
Adjusted p-value =	0.176	0.071	0.176	0.083
Carcinoma				
Incidence	1/43 ^c	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
Raw p-value =	- ^d	- ^d	- ^d	- ^d
Adjusted p-value =	- ^d	- ^d	- ^d	- ^d
Combined				
Incidence	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
Raw p-value =	0.242	0.052	0.275	0.108
Adjusted p-value =	0.275	0.209	0.275	0.215

Note: Trend test results denoted at control; * denotes significance at p=0.05.

- Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
- First adenoma in the study was observed at week 81 in the 940 mg/kg/day group.
- First carcinoma in the study was observed at week 105 in the controls.
- Trend p-value not reported since tumor incidence decreased with increasing dose.

Table 4.3. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague- Dawley Rats (MRID No. 41728701).								
Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59	-
Percentage (%)	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%	5.3%

2. Liver: Tumor incidences of liver tumors in male rats are presented in Tables 4.4. There was a statistically significant dose trend for liver adenomas; however, the trend was not statistically significant with an adjustment for multiple comparisons. Closer examination of the incidence indicates a relatively flat response at the low- and mid-dose with only an increase observed at the high-dose (940 mg/kg/day); however, the incidence of liver adenomas at the high-dose was not statistically significant when compared to the concurrent controls (raw or adjusted p-values). Carcinomas and combined adenomas/carcinomas lacked statistical significance in trend and pairwise comparisons (Table 4.4). Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range was 1.4%-18.3% (mean = 9.2%) for the adenomas and 0%-6.7% for carcinomas (mean = 2.6%). These data are provided in Table 4.5 and indicate that the observed incidences at all dose levels were within the historical control ranges. Except for a single animal at the mid-dose late in the study (89

weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were observed. Furthermore, there was no evidence of progression from adenomas to carcinomas.

Table 4.4. Hepatocellular Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990) Cochran-Armitage Trend Test & Fisher's Exact Test Results				
Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma Incidence (%) Raw p-value = Adjusted p-value =	2/44 ^a (5) 0.022* 0.089	2/45 (4) 0.700 0.700	3/49 (6) 0.551 0.700	7/48 ^b (15) 0.101 0.202
Carcinoma Incidence (%) Raw p-value = Adjusted p-value =	3/44 (7) - ^d - ^d	2/45 (4) - ^d - ^d	1/49 (2) - ^d - ^d	2/48 ^c (4) - ^d - ^d
Combined Incidence (%) Raw p-value = Adjusted p-value =	5/44 (11) 0.078 0.312	4/45 (9) 0.769 0.808	4/49 (8) 0.808 0.808	9/48 (19) 0.245 0.489

Note: Trend test results denoted at control; * denotes significance at p=0.05.

- Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
- First adenoma in the study was observed at week 88 in the 940 mg/kg/day group.
- First carcinoma in the study was observed at week 85 in the 940 mg/kg/day group.
- Trend p-value not reported since tumor incidence decreased with increasing dose.

Table 4.5. Historical Control Data — Hepatocellular Tumors in Male Sprague- Dawley Rats (MRID No. 41728701).								
Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Adenomas								
Tumor Incidence	5/60	11/68	1/70	3/59	11/60	5/60	4/60	-
Percentage (%)	8.3%	16.2%	1.4%	5.1%	18.3%	8.3%	6.7%	9.2%
Carcinomas								
Tumor Incidence	4/60	0/68	1/70	2/59	3/60	1/60	0/60	-
Percentage (%)	6.7%	0%	1.4%	3.4%	5%	1.7%	0%	2.6%

3. Thyroid: Tumor incidences of thyroid tumors in male and female rats are presented in Tables 4.6 and 4.7, respectively. For males, no statistically significant trends were observed for adenomas, carcinomas, or combined adenomas/carcinomas. For females, a statistically significant trend was observed for adenomas and combined adenomas/carcinomas; however, the trend was not statistically significant with adjustment for multiple comparisons. There was no statistical significance in pairwise analyses. Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range was 3.3%-10% (mean = 6.1%) for the adenomas and 0%-2.9% for carcinomas (mean = 0.9%). These data are provided in Table 4.8.

Non-neoplastic lesions (thyroid C-cell hyperplasia) were observed; however, there was a lack of a monotonic dose-response for these histopathological findings and no dose-related increase in severity to support tumor findings (Table 4.9). There was also no evidence of progression from adenomas to carcinomas.

Table 4.6. Thyroid C-Cell Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990) Cochran-Armitage Trend Test & Fisher's Exact Test Results				
Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma Incidence (%)	2/54 ^{a, b} (4)	4/55 (7)	8/58 (14)	7/58 (12)
Raw p-value =	0.079	0.348	0.060	0.099
Adjusted p-value =	0.132	0.348	0.132	0.132
Carcinoma Incidence (%)	0/54 (0)	2/55 ^c (4)	0/58 (0)	1/58 (2)
Raw p-value =	0.457	0.252	1.000	0.518
Adjusted p-value =	0.518	0.518	1.000	0.518
Combined Incidence (%)	2/54 (4)	6/55 (11)	8/58 (14)	8/58 (14)
Raw p-value =	0.087	0.141	0.060	0.060
Adjusted p-value =	0.116	0.141	0.116	0.116

Note: Trend test results denoted at control.

- a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
- b. First adenoma in the study was observed at week 54 in the controls.
- c. First carcinoma in the study was observed at week 93 in the 89 mg/kg/day group.

Table 4.7. Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend Test & Fisher's Exact Test Results (Stout and Ruecker, 1990).				
Tumor Type	0 mg/kg/day	113 mg/kg/day	457 mg/kg/day	1183 mg/kg/day
Adenoma Incidence (%)	2/57 ^a (4)	2/60 (3)	6/59 ^b (10)	6/55 (11)
Raw p-value =	0.040*	0.710	0.147	0.124
Adjusted p-value =	0.159	0.710	0.196	0.196
Carcinoma Incidence (%)	0/57 (0)	0/60 (0)	1/59 ^c (2)	0/55 (0)
Raw p-value =	0.494	1.000	0.509	1.000
Adjusted p-value =	0.509	1.000	0.509	1.000
Adenoma/Carcinoma Incidence (%)	2/57 (4)	2/60 (3)	7/59 (12)	6/55 (11)
Raw p-value =	0.042*	0.710	0.090	0.124
Adjusted p-value =	0.166	0.710	0.166	0.166

Note: Trend test results denoted at control; * denotes significant at p=0.05.

- a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
- b. First adenoma in the study was observed at week 72 in the controls.
- c. First carcinoma in the study was observed at week 93 in the 457 mg/kg/day group.

Table 4.8. Historical Control Data — Thyroid C-Cell Tumors in Female Sprague- Dawley Rats (MRID No. 41728701).								
Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Adenomas								
Tumor Incidence	2/60	3/69	7/70	3/59	5/59	5/60	2/60	-
Percentage (%)	3.3%	4.3%	10.0%	5.1%	8.5%	8.3%	3.3%	6.1%
Carcinomas								
Tumor Incidence	1/60	2/69	0/70	1/59	0/59	0/60	0/60	-
Percentage (%)	1.7%	2.9%	0%	1.7%	0%	0%	0%	0.9%

Table 4.9. Thyroid Non-Neoplastic Lesions (Stout and Ruecker, 1990)				
Males				
Dose	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Total Incidences of thyroid C-cell hyperplasia and severity scores	5/60 (8%) Diffuse (moderate) – 1 Multi-focal (minimal) – 3 Focal (mild) – 1	1/60 (2%) Focal (mild) – 1	6/60 (10%) Focal (minimal) – 4 Multi-focal (minimal) – 1 Multi-Focal (mild) – 1	5/60 (8%) Focal (minimal) – 2 Focal (mild) – 1 Multi-focal (mild) – 1 Multi-focal (moderate) – 1
Females				
	0 mg/kg/day	113 mg/kg/day	457 mg/kg/day	1183 mg/kg/day
Thyroid C-cell hyperplasia and severity scores	10/60 (17%) Diffuse (moderate) – 1 Focal (mild) – 1 Focal (minimal) – 1 Focal (mild) – 1 Focal (moderate) – 1 Multi-focal (minimal) – 3 Multi-focal (moderate) – 1 Diffuse (moderate) – 1	5/60 (8%) Focal (mild) – 3 Focal (minimal) – 1 Multi-focal (minimal) – 1	9/60 (15%) Focal (minimal) – 4 Multi-focal (minimal) – 2 Multi-focal (mild) – 3	5/60 (8%) Focal (mild) – 1 Focal (minimal) – 1 Multi-focal (mild) – 2 Diffuse (moderate) – 1

*Data taken from pages 1071-2114 of the study report.

4.5.3 Atkinson *et al.*, 1993a (MRID 49631701)¹⁸

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 Sprague-Dawley rats/sex/dose in the diet at doses of 0, 11/12, 112/109, 320/347, and 1147/1134 mg/kg/day for 104 weeks (M/F) for 104 weeks. An additional 35 rats/sex/dose were included for 1-year interim sacrifice.

¹⁸ Note: In Greim *et al.* (2015), the same study is cited as Cheminova (1993a).

No adverse effects on survival were seen in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidences in the study.

4.5.4 Brammer, 2001 (MRID 49704601)¹⁹

In a combined chronic toxicity/carcinogenicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 rats/sex received diets containing doses of 0, 121/145, 361/437 or 1214/1498 mg/kg/day for 24 months, in males/females, respectively. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSP 870.4200 and OCSP 870.4300).

A statistically significant higher survival ($p=0.02$) was observed in males at the highest dose tested at the end of 104 weeks relative to concurrent controls, and a statistically significant trend for improved survival was observed in treated males ($p=0.03$). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low-, mid-, and high-dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low-, mid- and high-dose groups, respectively. There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested. As shown in Table 4.10, a statistically significant trend in the incidences of liver adenomas was observed in male rats; however, a monotonic dose-response was not observed upon closer examination of the incidence data. Tumor incidences appear to fluctuate with increases observed at the low- and high-dose and no tumors observed in the control and mid-dose. Statistical significance with raw (unadjusted) p -values was observed for the tumor incidence at the high-dose (1214 mg/kg/day) when compared to concurrent controls; however, it was not statistically significant with an adjustment for multiple comparisons ($p=0.055$). The improved survival in the high-dose group may help explain a modestly higher incidence of an age-related background tumor like liver adenomas and this corresponds with the lack of associated lesions observed in the study.

Table 4.10. Liver Adenomas in Male Wistar Rats (Brammer, 2001) Cochran-Armitage Trend Test and Fisher's Exact Test Results.				
	0 mg/kg/day	121 mg/kg/day	361 mg/kg/day	1214 mg/kg/day
Adenoma Incidence (%)	0/44 ^a (0)	2/48 (4)	0/48 (0)	5/49 (10)
Raw p -value =	0.010*	0.269	1.000	0.037*
Adjusted p -value =	0.029*	0.269	1.000	0.055

Note: Trend test results denoted at control; * denotes significance at $p=0.05$; ** denotes significance at $p=0.01$
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

4.5.5 Pavkov and Wyand 1987 (MRIDs 40214007, 41209905, 41209907)

Glyphosate trimesium salt (sulfosate, 56.2% pure) was tested in a 2-year chronic feeding/carcinogenicity study in male and female Sprague-Dawley (CrI:CD[SD]BR) rats. Sixty

¹⁹ Note: In Greim *et al.* (2015), the same study is cited as Syngenta (2001).

animals/sex were tested in control group 1 (basal diet, no vehicle), 80/sex were tested in control group 2 (basal diet plus propylene glycol at 1% w/w vehicle) and in the low and mid-dose groups, and 90/sex were tested in the high dose group. The following dose levels were tested: 0, 4.2/5.4, 21.2/27 or 41.8/55.7 mg/kg/day in males and females respectively.

Treatment had no effect on survival. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidences in the study.

4.5.6 Suresh, 1996 (MRID 49987401)²⁰

In a combined chronic toxicity/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 6.3/8.6, 59.4/88.5, and 595.2/886 mg/kg/day glyphosate for 24 months in males and females respectively. The highest dose tested in females in this study approaches the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

No adverse effects on survival were observed in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.5.7 Enemoto, 1997 (MRID 50017103-50017105)²¹

In a combined chronic toxicity and carcinogenicity study, groups of 50 Sprague-Dawley rats/sex/group received daily dietary doses of 0, 104/115, 354/393 and 1127/1247 mg/kg bw/day glyphosate for males and females, respectively. In addition, 10 rats/sex/group were included for interim sacrifices at 26, 52, and 78 weeks. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

There were no changes in mortality at any of the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.5.8 Wood *et al.*, 2009a (MRID 49957404)²²

In a combined chronic toxicity/carcinogenicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 95.0, 316.9, and 1229.7 mg/kg/day glyphosate for males and female, respectively. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

²⁰ Note: In Greim *et al.* (2015), the same study is cited as Feinchemie Schwebda (1996).

²¹ Note: In Greim *et al.* (2015), the same study is cited as Arysta Life Sciences (1997b).

²² Note: In Greim *et al.* (2015), the same study is cited as NuFarm (2009b).

No adverse effects on survival were seen in either sex across the doses tested. There were no treatment-related preneoplastic or related non-neoplastic lesions in either sex at any dose level.

In female rats, mammary gland tumors were noted. Tumor incidences for mammary gland adenomas, adenocarcinomas, and combined adenomas/adenocarcinomas in female mice are presented in Table 4.11. Statistically significant trends were observed for the adenocarcinoma and combined analyses; however, statistical significance was only seen for the combined analyses following adjustment for multiple comparisons. There was no statistical significance observed in pairwise comparisons.

Table 4.11 Mammary Gland Tumor Incidences in Female Rats (Wood <i>et al.</i>, 2009a) Fisher's Exact Test and Cochran-Armitage Trend Test Results				
Tumor Type	0 mg/kg/day	95.0 mg/kg/day	316.9 mg/kg/day	1229.7 mg/kg/day
Adenoma				
Incidence	0/48 ^a	0/51	0/50	2/50
(%)	(0)	(0)	(0)	(4)
Raw p-value =	0.062	1.000	1.000	0.258
Adjusted p-value =	0.124	1.000	1.000	0.258
Adenocarcinoma				
Incidence	2/48	3/51	1/50	6/50
(%)	(4)	(6)	(2)	(12)
Raw p-value =	0.043*	0.529	0.886	0.148
Adjusted p-value =	0.172	0.705	0.886	0.296
Combined Incidence				
(%)	2/48	3/51	1/50	8/50
	(4)	(6)	(2)	(16)
Raw p-value =	0.007**	0.529	0.886	0.053
Adjusted p-value =	0.028*	0.705	0.886	0.105

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significant at p=0.01.

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

4.5.9 Summary of Rat Data

In 4 of the 8 rat studies conducted with glyphosate, no tumors were identified for evaluation. Of the remaining 4 rat studies, a statistically significant trend was observed for tumor incidences in the testes, liver, or mammary gland following adjustment for multiple comparisons. A statistically significant pairwise comparison was only observed following adjustment for multiple comparisons for testicular tumors at the highest dose tested (31 mg/kg/day) in one individual study. In some cases, the tumor incidence across doses did not demonstrate a monotonic dose response. There was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions or evidence of tumor progression (progression from pre-neoplastic to malignancy) to support biological significance of tumor findings. In a limited number of cases, the agency considered historical control data to inform the relevance of a tumor increase, which indicated concurrent controls were unusually low or the observed incidences were within the historical control range in most instances.

Table 4.12. Summary of Rat Carcinogenicity Studies			
Study	Dose Range	Pre-Neoplastic or Related Non-Neoplastic Lesions	Tumors Incidences, Statistical Significance, and Related Comments
Lankas (1981) Sprague-Dawley rats	98.7% Technical in diet 0, 3/3, 10/11, and 31/34 mg/kg/day [M/F]	None observed	Statistically significant trend observed for testicular interstitial cell tumors; however, did not observe monotonic dose-response with higher incidence at low-dose than mid-dose. Incidences were 0/47 in controls, 3/49 at low-dose, 1/47 at mid-dose, and 6/50 at high-dose. Increased incidence at high-dose statistically significant, but unusually low control incidence (based on terminal sacrifice historical control data in study report) inflated increase at high-dose.
Stout and Ruecker (1990) Sprague-Dawley rats	96.5% Technical in diet 0, 89/113, 362/457 and 940/1183 mg/kg/day [M/F] for 24 months	None observed	Pancreatic tumors lacked statistically significant trend. Tumor incidence for pancreatic adenomas in males were 1/43 in controls, 8/45 at the low-dose, 5/49 at the mid-dose, and 7/48 at the high-dose. Concurrent control incidence for this tumor type was at the lower bound of the historical control range for performing laboratory. Negative trend observed for carcinomas. Combined adenoma/carcinoma incidence similar except low-dose was 2/43. No statistically significant pairwise comparisons, including the highest dose tested which is approaching/exceeding 1,000 mg/kg/day. No statistically significant trends or pairwise comparisons for hepatocellular tumors following adjustment for multiple comparisons. Negative trend observed for carcinomas. The highest dose tested approached/exceeded 1,000 mg/kg/day. All incidences within historical control range for performing laboratory. No statistically significant trend for thyroid C-cell tumors in males. For females, statistically significant trend for combined adenomas/carcinomas following adjustment for multiple comparisons. Incidences for combined adenomas/carcinomas were 2/57 in controls, 2/60 at the low-dose, 7/59 at the mid-dose, and 6/55 at the high-dose. No statistically significant pairwise comparisons, including the highest dose tested which is approaching/exceeding 1,000 mg/kg/day.
Atkinson <i>et al.</i> (1993a) Sprague-Dawley rats	98.9% Technical in diet 0, 11/12, 112/109, 320/347, and 1147/1134 mg/kg/day for 104 weeks (M/F)	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.

Table 4.12. Summary of Rat Carcinogenicity Studies			
Study	Dose Range	Pre-Neoplastic or Related Non-Neoplastic Lesions	Tumors Incidences, Statistical Significance, and Related Comments
Brammer (2001) Wistar rats	97.6% Technical in diet 0, 121/145, 361/437 and 1214/1498 mg/kg/day [M/F]	None observed	Statistically significant trend in liver adenomas in males. Non-monotonic dose-response with incidences at 0/44 in controls, 2/48 at the low-dose, 0/48 at the mid-dose, and 5/49 at the high-dose. No statistically significant pairwise comparisons following adjustment for multiple comparisons, including the highest dose tested which exceeded 1,000 mg/kg/day.
Pavkov and Wyand (1987) Sprague-Dawley rats	56.2% Technical (Trimesium salt; Sulfosate) 0, 4.2/5.4, 21.2/27 and 41.8/55.7 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation.
Suresh (1996) Wistar rats	96.0-96.8% Technical in diet 0, 6.3/8.6, 59.4/88.5, and 595.2/886 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.
Enemoto (1997) Sprague-Dawley rats	94.61-97.56% Technical in diet 0, 104/115, 354/393 and 1127/1247 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.
Wood <i>et al.</i> (2009a) Wistar rats	95.7% Technical in diet 0, 86/105, 285/349 or 1077/1382 mg/kg/day [M/F]	None observed	Statistically significant trends were observed for the combined mammary gland adenoma/adenocarcinoma analyses following adjustment for multiple comparisons. Incidences were 2/48 in controls, 3/51 at the low-dose, 1/50 at the mid-dose, and 8/50 at the high-dose. No statistically significant pairwise comparisons, including the highest dose tested which exceed 1,000 mg/kg/day.

4.6 Mouse Carcinogenicity Studies with Glyphosate

4.6.1 Reyna and Gordon, 1973 (MRID 00061113)

In an 18-month carcinogenicity study, groups of 50 Swiss white mice/sex/dose were fed glyphosate at dietary levels of approximately 17 mg/kg/day and 50 mg/kg/day. There was no effect on survival at any of the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study. Although only ten mice/sex/dose were examined for histopathological changes, there were no statistically significant increases in tumors observed in the study; therefore, this deficiency would not impact the overall conclusion regarding tumor findings.

4.6.2 Knezevich and Hogan, 1983 (MRID 00130406)²³

Groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary doses of 0, 161/195, 835/968, 4945/6069 mg/kg/day for males and females, respectively for 24 months. The highest dose tested in this study far exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Furthermore, the mid-dose tested in this study was approaching 1,000 mg/kg/day. Tumor findings at these high doses are given less weight. No effect on survival was observed. A low incidence of renal tubule adenomas, which are considered rare, were noted in males. The incidences of renal tubule adenomas following initial evaluation of the study were reported as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR# 0004370). In 1985, the registrant directed a re-evaluation of the original renal sections by a consulting pathologist. This re-evaluation identified a small renal tubule adenoma in one control male mouse, which was not diagnosed as such in the original pathology report. In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related.

Subsequently, the agency requested a Pathology Work Group (PWG) evaluate the kidney sections. The PWG examined all sections of the kidney, including the additional renal sections, and were blinded to treatment group. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 4.13 with results from statistical analyses. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it is appropriate to combine the incidences from these two tumor types for purposes of evaluation and statistical analysis. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the concurrent controls and there was no evidence of a statistically significant linear trend; 3) multiple renal tumors were not found in any

²³ Note: In Greim *et al.* (2015), the same study is cited as Monsanto (1983).

animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study (TXR# 0005590).

Table 4.13. Renal Tubular Cell Tumors in Male CD-1 Mice (Knezevich and Hogan, 1983) Cochran-Armitage Trend Test & Fisher's Exact Test Results.				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenoma Incidence (%)	1/49 (2)	0/49 (0)	0/50 (0)	1/50 (2)
Raw p-value =	0.442	1.000	1.000	0.758
Adjusted p-value =	1.000	1.000	1.000	1.000
Carcinoma Incidence (%)	0/49 (0)	0/49 (0)	1/50 (2)	2/50 (4)
Raw p-value =	0.063	1.000	0.505	0.253
Adjusted p-value =	0.190	1.000	0.505	0.379
Combined Incidence (%)	1/49 (2)	0/49 (0)	1/50 (2)	3/50 (6)
Raw p-value =	0.065	1.000	0.758	0.316
Adjusted p-value =	0.259	1.000	1.000	0.633

Note: Trend test results denoted at control.

Historical control data from 14 studies conducted between 1977 and 1981 (within <1 to 3 years of when Knezevich and Hogan (1983) was performed) at the performing laboratory (Table 4.14) indicated that the mouse renal tubular adenomas ranged from 0 to 3.3% and the incidence in the current study was within the historical control range (TXR# 0007252).

Table 4.14. Historical Control Data- Kidney tumors in CD-1 Mice (TXR #0007252).														
Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77- 4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma	0	1	0	0	0	0	0	0	0	2	0	0	0	0

Histopathological examinations noted chronic interstitial nephritis and tubular epithelial changes (basophilia and hypertrophy) in the kidneys of male rats in the study (Table 4.15). The increased incidence of chronic interstitial nephritis in males lacked a dose-response. The incidence in controls of bilateral interstitial nephritis was higher than low-dose group and approximately the same as the mid-dose group. Unilateral chronic interstitial nephritis was only seen in 1 animal in the low- and high-dose groups. Furthermore, chronic interstitial nephritis is not considered to be a precursor lesion for tubular neoplasms. A monotonic dose-response was not observed for the epithelial basophilia and hypertrophy, such that the incidence fluctuated with dose and the lowest incidence was observed at the highest dose tested. There was no increase in supporting preneoplastic or related non-neoplastic renal tubular lesions (e.g., tubular epithelial necrosis/regeneration, hyperplasia) observed in male mice.

Table 4.15. Kidney Histopathological Alterations in Male CD-1 Mice (Knezevich and Hogan, 1983)				
Males				
Dose	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Bilateral Chronic Interstitial Nephritis	5/49 (10%)	1/49 (2%)	7/50 (14%)	11/50 (22%)
Unilateral Chronic Interstitial Nephritis	0/49 (0%)	1/49 (2%)	0/49 (0%)	1/50 (2%)
Proximal Tubule Epithelial Basophilia and Hypertrophy	15/49 (31%)	10/49 (20%)	15/50 (30%)	7/50 (14%)

*Data taken from page 305 and 306, and the study pathology report; incidences were moderate diffuse

4.6.3 Atkinson, 1993b (MRID 49631702)²⁴

In a carcinogenicity study, glyphosate (>97% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet for 104 weeks at doses of 0, 98/102, 297/298, 988/1000 mg/kg/day for males and females, respectively. No interim sacrifices were performed.

There was no effect on survival in the study. There were no preneoplastic lesions or related non-neoplastic lesions observed. As shown in Table 4.16, hemangiosarcomas were found in 4/45 (9%) of high-dose male mice (1000 mg/kg/day) compared to none in the concurrent controls or other treated groups. Hemangiosarcomas are commonly observed in mice (generally more common in males for CD-1 strain) as both spontaneous and treatment-related tumors arising from endothelial cells. As vascular tumors, they can occur at different sites, with liver and spleen tending to be the most common sites in mice. In the high-dose mice with hemangiosarcomas, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. A statistically significant trend was observed. Closer examination of the incidence indicates a relatively flat response at the low- and mid-dose with only an increase observed at the high-dose; however, the incidence of hemangiosarcomas at the high-dose was not statistically significant when compared to the concurrent controls.

Table 4.16. Hemangiosarcomas in Male CD-1 Mice (Atkinson, 1993b)				
Cochran-Armitage Trend Test and Fisher's Exact Test Results.				
Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcoma Incidence (%)	0/47 ^a (0)	0/46 (0)	0/50 (0)	4/45 (9)
Raw p-value =	0.003**	1.000	1.000	0.053
Adjusted p-value =	0.006**	1.000	1.000	0.053

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.

²⁴ Note: In Greim *et al.* (2015), the same study is cited as Cheminova (1993b).

4.6.4 Wood *et al.*, 2009b (MRID 49957402)²⁵

In a feeding study, CD-1 mice (50/sex/dose) received glyphosate (95.7%) for 80 weeks at dietary dose levels of 0, 71.4/97.9, 234.2/299.5, or 810/1081.2 mg/kg/day for males and females, respectively. The highest dose tested in this study approaches or exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

There was no effect on survival in the study. In male mice at the high dose, there were increases in the incidences of lung adenocarcinomas and malignant lymphomas. A discussion of each tumor type is presented below:

1. Lung: Tumor incidence for lung adenomas, adenocarcinomas, and combined adenomas/adenocarcinomas are presented in Table 4.17. A statistically significant trend was only noted for the adenocarcinomas; however, the trend was not statistically significant with adjustment for multiple comparisons. Closer examination of the tumor incidence indicates the dose-response was relatively flat at the low- and mid-dose with only an increase observed at the high-dose and the incidence of lung adenocarcinomas at the high-dose (810 mg/kg/day) was not statistically significant when compared to the concurrent controls. There were no treatment-related preneoplastic or related non-neoplastic lesions observed.
2. Malignant lymphoma: Tumor incidence for malignant lymphoma are also presented in Table 4.18. A statistically significant trend was observed and the incidence at the high-dose (810 mg/kg/day) was statistically significantly elevated as compared to concurrent controls with the raw (unadjusted) p-value; however, with an adjustment for multiple comparisons, the increased incidence at the high-dose was not statistically significant ($p=0.059$). Historical control data have been submitted (MRIDs 50464501 and 50464601) from the same testing laboratory for 10 studies of similar duration. These data were generated within approximately 5 years of the Wood *et al.* (2009b) study. The historical control range was 0%-32% (mean = 8.7%). All observed incidences of this tumor type were within the historical control range.

²⁵ Note: In Greim *et al.* (2015), the same study is cited as NuFarm (2009a).

Table 4.17. Lung Tumors in Male CD-1 Mice (Wood <i>et al.</i>, 2009b) Fisher's Exact Test and Cochran-Armitage Trend Test Results.				
Dose (mg/kg/day)	0	71.4	234.2	810
Lung Adenoma Incidence (%)	9/44 (20)	7/46 (15)	9/48 (19)	4/45 (9)
Raw p-value =	_{-b}	_{-b}	_{-b}	_{-b}
Adjusted p-value =	_{-b}	_{-b}	_{-b}	_{-b}
Lung Adenocarcinoma (%)	5/44 ^a (11)	5/46 (11)	7/48 (15)	11/45 (24)
Raw p-value =	0.026*	0.659	0.443	0.091
Adjusted p-value =	0.103	0.659	0.590	0.182
Lung Combined Incidence (%)	14/44 (32)	12/46 (26)	16/48 (33)	15/45 (33)
Raw p-value =	0.328	0.797	0.527	0.529
Adjusted p-value =	0.706	0.797	0.706	0.706

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).

b = Trend and pairwise p-values not reported since tumor incidence decreased with increasing dose.

Table 4.18. Malignant Lymphomas in Male CD-1 Mice (Wood <i>et al.</i>, 2009b) Fisher's Exact Test and Cochran-Armitage Trend Test Results.				
Dose (mg/kg/day)	0	71.4	234.2	810
Malignant Lymphoma Incidence (%)	0/44 (0)	1/46 (2)	2/48 (4)	5/45 (11)
Raw p-value =	0.006**	0.511	0.269	0.029*
Adjusted p-value =	0.025*	0.511	0.359	0.059

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).

4.6.5 Sugimoto, 1997 (MRID 50017108 - 50017109)²⁶

In a carcinogenicity study, glyphosate (purity 97.56 and 94.61%; two lots) was administered to groups of 50 male and 50 female Specific-Pathogen-Free (SPF) ICR (Crj: CD-1) mice/dose in the diet at dose levels of 0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg/day for males and females, respectively, for 18 months. The highest dose tested in this study far exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Furthermore, the mid-dose tested in this study was approaching 1,000 mg/kg/day. Tumor findings at these high doses are given less weight.

²⁶Note: In Greim *et al.* (2015), the same study is cited as Arysta Life Sciences (1997b)

There were no treatment-related effects on mortality or survival. There were no changes in histopathological findings observed.

Hemangiomas in female mice were found to occur at different sites. The tumor incidences are presented in Table 4.19. A statistically significant trend was observed. Tumor incidence at the high-dose, which was approximately 4 times the recommended high-dose in test guidelines (4116 mg/kg/day), was statistically significant as compared to concurrent controls.

Table 4.19. Hemangioma Incidences (Sugimoto, 1997) Fisher's Exact Test and Cochran-Armitage Trend Test Results				
Tumor Type	0 mg/kg/day	153.2 mg/kg/day	786.8 mg/kg/day	4116 mg/kg/day
Hemangioma Incidence (%)	0/48 (0)	0/47 (0)	2/45 (4)	5/45 (11)
Raw p-value =	0.002**	1.000	0.231	0.024*
Adjusted p-value =	0.005**	1.000	0.231	0.035*

Note: Trend test results denoted at control; * denotes significance at $p=0.05$; ** denotes significance at $p=0.01$.

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).

4.6.6 Pavkov and Turnier, 1987 (MRIDs 40214006, 41209907)

Glyphosate trimesium salt (sulfosate, 56.2% pure) was tested in a 2-year chronic feeding/carcinogenicity study in male and female CD-1 mice. Sixty animals/sex were tested in control group 1 (basal diet, no vehicle), 80/sex were tested in control group 2 (basal diet plus propylene glycol at 1% w/w vehicle) and in the low- and mid-dose groups, and 90/sex were tested in the high-dose group. The following dose levels were tested: 0, 11.7/16, 118/159, and 991/1341 mg/kg/day for males and females, respectively.

No adverse effects on survival were seen in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.6.7 Summary of Mouse Data

No tumors were identified for evaluation in 2 of the 6 mouse carcinogenicity studies. In the remaining 4 mouse studies, 3 observed a statistically significant trend in tumor incidences in the hemangiosarcomas, malignant lymphomas, or hemangiomas following adjustment for multiple comparisons. In one individual study, a statistically significant pairwise comparison was only observed following adjustment for multiple comparisons for hemangiomas at the highest dose tested, which was more than 4X the limit dose. There was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions or evidence of tumor progression (progression from pre-neoplastic to malignancy) to support biological significance of tumor findings. In a limited number of cases, historical control data were available which the observed tumor incidences were within the historical control range.

Table 4.20. Summary of Mouse Carcinogenicity Studies			
Study	Dose Range	Pre-Neoplastic or Related Non-Neoplastic Lesions	Tumors Incidences, Statistical Significance, and Related Comments
Reyna and Gordon (1973) Swiss white mice	0, 17 or 50 mg/kg/day for 18 months	None observed	There were no tumors identified for evaluation.
Knezevich and Hogan (1983) CD-1 mice	99.78% Technical in diet 0, 161/195, 835/968, 4945/6069 mg/kg/day for [M/F] for 24 months.	Chronic interstitial nephritis lacked dose-response and not considered relevant to renal tumors. Tubular epithelial changes in kidney were approximately the same in controls, low- and mid-doses and then decreased at high-dose.	No statistical significance in trend or pairwise comparisons, including the mid- and high-doses which approached or exceeded 1,000 mg/kg/day. Incidence of adenomas within historical control range for performing laboratory.
Atkinson <i>et al.</i> (1993b). CD-1 mice	97.5 - 100.2% Technical in diet 0, 98/102, 297/298, 988/1000 mg/kg/day for 104 weeks (M/F)	None observed	Statistically significant trend for hemangiosarcomas that were only observed in 4/45 (9%) high-dose male mice. Increased incidence was not statistically significant from the concurrent controls at all doses, including the highest dose tested which is approximately 1,000 mg/kg/day.
Wood <i>et al.</i> (2009b) CD-1 mice	95.7% Technical in diet 0, 71.4/97.9, 234.2/299.5, or 810/1081.2 mg/kg/day [M/F] for 80 weeks	None observed	No statistically significance in trend or pairwise comparisons following adjustment for multiple comparisons. Negative trend observed for adenomas. Statistically significant trend for malignant lymphoma with incidences of 0/44 in controls, 1/46 at the low-dose, 2/48 at the mid-dose, and 5/45 at the high-dose. No statistically significant pairwise results following adjustment for multiple comparisons, including the highest dose tested which was approaching 1,000 mg/kg/day. All observed incidences within historical control range for performing laboratory.

Table 4.20. Summary of Mouse Carcinogenicity Studies			
Study	Dose Range	Pre-Neoplastic or Related Non-Neoplastic Lesions	Tumors Incidences, Statistical Significance, and Related Comments
Sugimoto (1997) CD-1 mice	94.61 – 97.56% Technical in diet 0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg/day [M/F] for 18 months	None observed	Statistically significant trend for hemangiomas in female mice following adjustment for multiple comparisons with incidences of 0/48 in controls, 0/47 at the low-dose, 2/45 at the mid-dose, and 5/45 at the high-dose. Increased incidence at high-dose statistically significant following adjustment for multiple comparisons. Highest dose tested was more than 4X the limit dose.
Pavkov and Turnier (1987) CD-1 mice	56.2% Technical (Trimesium salt; Sulfosate) 0, 11.7/16, 118/159, and 991/1341 mg/kg/day [M/F] for 24 months.	None observed	There were no tumors identified for evaluation, including the highest dose tested which approached/exceeded 1,000 mg/kg/day.

4.7 Absorption, Distribution, Metabolism, Excretion (ADME)

The 2005 EPA Guidelines for Carcinogen Risk Assessment also permit analysis of other key data that may provide valuable insights into the likelihood of human cancer risk from exposure to a chemical, such as information regarding the absorption, distribution, metabolism, and excretion (ADME) of a test chemical. EPA's Harmonized Test Guidelines for pesticides include a series of studies for characterizing a chemical's metabolism and pharmacokinetics. As described in the test guideline (OCSPP 870.7485), testing of the disposition of a test substance is designed to obtain adequate information on its: absorption, distribution, biotransformation (metabolism), and excretion, which can all collectively aid in understanding the chemical's mechanism of toxicity. Basic pharmacokinetic/toxicokinetic parameters determined from these studies can also provide information on the potential for accumulation of the test substance in tissues and/or organs and the potential for induction of biotransformation as a result of exposure to the test substance. These data can be used to assess the adequacy and relevance of the extrapolation of animal toxicity data (particularly chronic toxicity and/or carcinogenicity data) to estimate human risk.

Oral exposure is considered the primary route of concern for glyphosate. The maximum absorption from the GI tract for glyphosate was estimated to be ~30% with one study showing up to 40% based upon radiolabel detected in the urine. In general, the amounts of glyphosate detected in tissues were negligible indicating low tissue retention following dosing. Parent glyphosate is the principal form excreted in urine and feces. The primary route of excretion following oral administration of glyphosate is the feces, as verified by the intravenous dosing and bile cannulation experiments. Within the dose ranges tested, elimination was essentially complete by 24 hours indicating that glyphosate does not bioaccumulate.

Multiple studies examined the pharmacokinetics of a single dose of radiolabeled glyphosate ranging from 5.6 – 400 mg/kg. Across these studies, time to reach peak plasma concentrations (T_{max}) appeared to increase with increasing dose; however, the reported range of T_{max} (1-5.5 hours) suggests only a slight shift in absorption kinetics occurs despite large increases in dose. In the one study that tested two doses (NTP, 1992), data graphically show that peak blood levels were only roughly 3-fold with a 10-fold increase between the two doses. Reported area under the curve (AUC) values indicated conflicting results regarding whether linear or non-linear absorption kinetics was occurring at higher doses.

In general, EPA and OECD guideline ADME studies are designed for a different purpose and do not provide the information needed to adequately determine whether linear kinetics is still occurring at high doses of glyphosate. These studies are often limited to one or two doses and do not include time course data. A well-conducted pharmacokinetic study testing multiple doses is needed to conclusively make this determination.

4.8 Discussion

Glyphosate has been extensively tested in rodents to evaluate its carcinogenic potential. A total of 14 rodent carcinogenicity studies were considered to be adequate for this analysis. Eight studies were conducted in the rat and 6 studies were conducted in the mouse. When a potential tumor signal was identified in a study, the agency considered several factors. Consistent with the EPA's 2005 Guidelines for Carcinogen Risk Assessment, the agency evaluated the tumor responses for both statistical and biological significance by considering factors such as historical control data; rarity of tumor types; tumors at multiple sites; tumors in multiple species, strains, or both sexes; progression of lesions from preneoplastic to benign to malignant; reduced latency of neoplastic lesions (i.e., time to tumor); presence of metastases; unusual magnitude of tumor response; proportion of malignant tumors; and dose-related increases. When these factors were considered together, the agency made a determination of whether or not the observed tumor was related to treatment with glyphosate. A weight of the evidence approach was used to determine the carcinogenic potential of glyphosate in rodents.

In 4 of the 8 rat studies conducted with glyphosate, no tumors were identified for evaluation. Of the remaining 4 rat studies, tumor incidences were evaluated in detail for testicular, pancreatic, hepatocellular, thyroid C-cell, and mammary gland tumors. In 2 of the 6 mouse studies, no tumors were identified for evaluation. In the remaining 4 mouse studies, tumor incidences were evaluated in detail for hemangiosarcomas, malignant lymphoma, hemangiomas, lung, and kidney tumors. Below are the weight of evidence evaluations for each tumor type.

Testicular Tumors

In Table 4.1, a statistically significant trend was observed for testicular interstitial cell tumors (adjusted p-value = 0.032) and pairwise significance was observed at the highest dose tested of 31 mg/kg/day (adjusted p-value = 0.032) in male Sprague-Dawley rats (Lankas, 1981). Closer examination of the tumor incidence indicated that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. It was also noted that the incidence of testicular cell tumors in concurrent controls (0%) appears to be unusually low for this tumor type as compared to historical controls from the performing laboratory. These data also indicated that the incidence at the highest dose tested was outside the historical control range when all animals were considered, but within the terminal historical control range for the performing laboratory. Testicular interstitial cell tumors are relatively common in Sprague-Dawley rats and this tumor type is difficult to distinguish from simple hyperplasia. Testicular tumors were not seen in the other 7 rat studies, many of which tested up to or beyond the limit dose (1000 mg/kg/day). More specifically, of the 4 other studies performed in Sprague-Dawley rats (Stout and Ruecker, 1990; Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997), 3 were tested at doses 30X higher or more than the highest dose tested in Lankas (1981) and no testicular tumors were observed. Furthermore, there were no testicular tumors observed in the 6 mouse bioassays.

Pancreatic Tumors

In Table 4.2, no statistically significant trends were observed for pancreatic islet cell tumors in male Sprague-Dawley rats (Stout and Ruecker, 1990). Raw p-values were statistically

significant for adenomas at the low and high dose for pairwise comparisons; however, these were not statistically significant following adjustment for multiple comparisons. Closer examination of the tumor incidence indicated that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose and high-dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Historical control data from the performing laboratory for pancreatic adenomas indicated that the incidence in concurrent controls was at the lower limit of the historical control range. There was no evidence of progression to malignancy. Notably, carcinomas demonstrated a negative trend with decreasing tumor incidence with increasing dose. Pancreatic tumors were not observed in the other 7 rat studies, including 4 other studies performed in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981). Furthermore, pancreatic tumors were not observed in the 6 mouse bioassays.

Hepatocellular Tumors

Hepatocellular tumors were evaluated in 2 rat carcinogenicity studies (Stout and Ruecker, 1990; Brammer, 2001). In Table 4.4, the raw p-value for trend was statistically significant for adenomas in male Sprague-Dawley rats (Stout and Ruecker, 1990); however, it was not statistically significant following adjustment for multiple comparisons. There were no statistically significant pairwise comparisons. Historical control data from the performing laboratory indicated that the incidence of hepatocellular tumors was within the historical control range at all doses. Closer examination of the tumor incidence indicated that the data fluctuated with no tumors observed in concurrent controls or the mid-dose and increases seen at the low-dose and high-dose. In Table 4.10, a statistically significant trend was observed for adenomas in male Wistar rats (adjusted p-value = 0.029) (Brammer, 2001). For pairwise comparisons, the raw p-value was statistically significant at the highest dose tested (1214 mg/kg/day); however, it was not statistically significant following adjustment for multiple comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect in both studies. There was no evidence of progression to malignancy. In particular, carcinomas demonstrated a negative trend with decreasing tumor incidence with increasing dose. Hepatocellular tumors were not observed in the other 6 rat studies, including 4 other studies in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981) and 2 other studies in Wistar rats (Suresh, 1996; Wood *et al.* 2009a) the same rat strains. Furthermore, hepatocellular tumors were not observed in the 6 mouse bioassays.

Thyroid Tumors

In Table 4.6, there were no statistically significant trends or pairwise comparisons were observed for thyroid C-cell tumors in male Sprague-Dawley rats (Stout and Ruecker, 1990). In Table 4.7, a statistically significant trend for adenomas and combined adenomas/carcinomas was observed with raw p-values in female Sprague-Dawley rats (Stout and Ruecker, 1990); however, the trends were not statistically significant with adjustment for multiple comparisons. There were no statistically significant pairwise comparisons observed at any dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Thyroid tumors were not observed in the other 7 rat studies, including 4 other studies performed in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981). Furthermore, thyroid tumors were not observed in the 6 mouse bioassays.

Mammary Gland Tumors

In Table 4.11, raw trend p-values were statistically significant for mammary gland adenocarcinomas and combined adenomas/adenocarcinomas in female Wistar rats (Wood *et al.*, 2009a); however, only the combined p-value for trend remained statistically significant following adjustment for multiple comparison (adjusted p-value = 0.028). There were no statistically significant pairwise comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Mammary gland tumors were not observed in the other 7 rat studies, including 2 other studies performed in Wistar rats (Brammer, 2001; Suresh, 1996). Furthermore, mammary gland tumors were not observed in the 6 mouse bioassays.

Kidney Tumors

In Table 4.13, there were no statistically significant trend observed for renal tubular cell tumors in male CD-1 mice (Knezevich and Hogan, 1983). This study tested up to almost 5000 mg/kg/day. Historical control data from the performing laboratory indicated that the incidence of adenomas was within the historical control range. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Kidney tumors were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Atkinson *et al.*, 1993b; Wood *et al.*, 2009b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, kidney tumors were not observed in the 8 rat bioassays.

Hemangiosarcomas

In Table 4.16, a statistically significant trend was observed for hemangiosarcomas in male CD-1 mice (adjusted p-value = 0.006) (Atkinson *et al.*, 1993b). There were no statistically significant pairwise comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Hemangiosarcomas are commonly observed in mice (generally more common in males for CD-1 strain) as both spontaneous and treatment-related tumors arising from endothelial cells. Hemangiosarcomas were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Wood *et al.*, 2009b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, hemangiosarcomas were not observed in the 8 rat bioassays.

Lung Tumors

In Table 4.17, the raw p-value for trend was observed for lung adenocarcinomas; however, the trend was not statistically significant following adjustment for multiple comparisons in male CD-1 mice (Wood *et al.*, 2009b). There were no statistically significant pairwise comparisons. Tumor incidences at all doses were within the historical control range for the performing laboratory. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Lung tumors were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, lung tumors were not observed in the 8 rat bioassays.

Malignant Lymphoma

In Table 4.18, statistically significant trend was observed in male CD-1 mice (adjusted p-value = 0.025) (Wood *et al.*, 2009b). For pairwise comparisons, the raw p-value for the highest dose tested was statistically significant; however, it was not statistically significant following adjustment for multiple comparisons. Malignant lymphoma was not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, malignant lymphoma was not observed in the 8 rat bioassays.

Hemangiomas

In Table 4.19, a statistically significant trend was observed in female CD-1 mice (adjusted p-value = 0.005) (Sugimoto, 1997). For pairwise comparisons, the incidence at the highest dose tested was statistically significant (adjusted p-value = 0.035). The highest dose tested in this study was more than 4X the limit dose. Hemangiomas were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Wood *et al.*, 2009b; Pavkov and Turnier, 1987). Furthermore, hemangiomas were not observed in the 8 rat bioassays.

Based on the weight-of-evidence evaluations, the agency has concluded that none of the tumors evaluated in individual rat and mouse carcinogenicity studies are treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Tumors seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses.

5.0 Data Evaluation of Genetic Toxicity

5.1 Introduction

Genotoxicity is a broad term for any damage to the genetic material, whether the damage is transient or permanent. Transient damage refers to unintended modifications to the structure of DNA, which may or may not undergo successful repair. Permanent damage refers to heritable changes in the DNA sequence, known as mutations. Types of mutations include: 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 (OECD, 2015). In somatic cells, DNA-reactive chemicals can cause cancer if the mutations occur within regulatory genes that control cell growth, cell division and differentiation, such as proto-oncogenes, tumor suppressor genes and/or DNA damage response genes (OECD, 2015). Additionally, DNA damage may signal the cell to undergo apoptosis (cell death) rather than cell division and, therefore, the damage is not “fixed” as a mutation and is not passed along to daughter cells.

Evaluation of genotoxicity data entails a weight-of-evidence approach that includes consideration of the various types of genetic damage that can occur. Since no single genotoxicity assay evaluates the many types of genetic alterations that can be induced by a chemical, one must employ a battery of genotoxicity tests to adequately cover all the genetic endpoints important for regulatory decisions. EPA, like other regulatory agencies, considers genotoxicity information as part of the weight of evidence when assessing the potential of a chemical to induce cancer in humans. Under FIFRA, OPP requires genotoxicity tests of the technical grade active ingredient for the registration of both food and non-food use pesticides. The current genotoxicity test battery (40 CFR Part 158.500) for pesticide registration consists of:

- 1) Bacterial reverse mutation test (typically conducted in bacteria strains *Salmonella typhimurium* and *Escherichia coli*),
- 2) *in vitro* mammalian (forward) gene mutation *and in vitro* mammalian chromosomal aberration test, and
- 3) *in vivo* test for micronucleus induction (mammalian erythrocyte micronucleus test) *or in vivo* chromosomal aberration test (mammalian bone marrow chromosomal aberration test).

In cases where equivocal or inconsistent results are obtained for the same endpoint in different test systems, additional testing may be required. Test Guidelines on how to conduct the genotoxicity tests have been published by the agency and have been harmonized with the Organization for Economic Cooperation and Development (OECD, 2015; Cimino 2006). These guidelines identify specific test species, genetic endpoints, test conditions, exposure durations as well information on how to report data and interpret the results. The test guidelines provide a level of consistency and predictability for regulatory compliance and regulatory decision making.

5.2 Scope of the Assessment Considerations for Study Quality Evaluation

Previous genotoxicity assessments conducted as part of the CARC reviews for glyphosate in 1991 and 2015, considered only studies conducted with glyphosate technical and included only studies that provided adequate characterization of the test material (*i.e.* purity information provided). In the current analysis, a fit-for-purpose systematic review process was conducted to identify relevant genotoxicity data from regulatory studies and published literature from open sources (published and unpublished) for both glyphosate technical and glyphosate-based formulations. Studies conducted with glyphosate formulations that were identified and considered relevant for genotoxicity evaluation are summarized in table form in Appendix F. As described in Section 7.0 of this document, glyphosate formulations are hypothesized to be more toxic than glyphosate alone. The agency is collaborating with NTP to systematically investigate the mechanism(s) of toxicity for glyphosate and glyphosate formulations. However, the focus of this section is the genotoxic potential of glyphosate technical.

As described previously in Section 2.1.3, the list of studies identified in this process were also cross-referenced with genotoxicity review articles for glyphosate from the open literature [Kier and Kirkland (2013), and Williams *et al.* (2000)], as well as recent international evaluations of glyphosate (IARC 2015, EFSA 2015, JMPR 2016). The current analysis also includes studies conducted by other registrants that were not previously available to the agency. Sixteen studies for glyphosate technical that were included in Kier and Kirkland (2013) were not available to the agency; therefore, data and study summaries provided in the review articles were relied upon in the current review and are identified in the data tables with a footnote. The Kier and Kirkland (2013) article serves as the original publication for these studies and provided relevant information on study design and conditions as well as summary data. The data set includes *in vitro* and *in vivo* studies conducted in mammalian systems, with the exception of standard bacterial test strains, which have a long history of detecting chemicals that are mutagenic in humans. Studies conducted in non-mammalian species (e.g. worms, fish, reptiles, plants), were excluded because they were considered to be not relevant for informing genotoxic risk in humans. Several epidemiological studies that evaluated biomarkers for genotoxicity were not included in this evaluation because these studies were assigned a low quality ranking as described in Section 3.3.

When evaluating the quality of the published and unpublished data for inclusion in the analysis, the agency considered the reporting quality (how well a study was reported), the study design and how well the study was conducted. Critical elements in study design and interpretation for genotoxicity tests are described in the various EPA and OECD test guidelines. Elements such as test conditions (e.g. solubility, pH, osmolarity, and cytotoxicity) and study design (e.g. number of test organisms, doses selected, use of positive and negative controls; blinded evaluation) were used to evaluate the quality of published and non-published studies. In cases where inappropriate testing conditions or study design clearly had an impact on the outcome the study, the study was excluded from the analysis. For example, early studies by Majeska (1982) were excluded from the analysis since it was clearly demonstrated that altered pH by the test chemical can result in false positive responses in several of *in vitro* genotoxicity tests (Majeska, 1985d,e,f). In other cases, particularly with the published literature studies, where test conditions and/or study design differed from what is generally considered as acceptable

following in the EPA or OECD guidelines, the differences are noted, but the studies were not excluded from analysis unless the condition made the study unreliable. Summaries of relevant genotoxicity studies can be found in TXR# 0057499. Studies that were excluded from the analysis are listed in Appendix G.

The studies evaluating the genetic toxicity of the active ingredient glyphosate are presented in the following sections according to the type of genetic endpoints evaluated: mutations, chromosomal aberrations and other assays evaluating DNA damage. *In vitro* and *in vivo* assays are discussed separately according to the genetic endpoint. For the purpose of this analysis, glyphosate and its salts are considered together when evaluating the genotoxic potential of the active ingredient glyphosate.

5.3 Tests for Gene Mutations for Glyphosate Technical

5.3.1 Bacterial Mutagenicity Assays

Bacteria have traditionally been employed as a primary test organism for the detection of chemical mutagens. The bacterial reverse mutation assay is routinely performed in the test strains of *Salmonella typhimurium* and *Escherichia coli*. These test strains are mutant strains that are deficient for the synthesis of an essential amino acid. The assay detects mutations that revert the test strains back to wild type for amino acid synthesis and the revertants are identified by their ability to grow in culture medium deficient of the specific amino acid(s). This mutagenicity test identifies point mutations, which includes base substitutions and deletions and insertions of up to a few base pairs (OECD 471). The tests are typically conducted in the presence and absence of an exogenous source of metabolic activation (e.g., S9 microsomal fraction of activated liver homogenates) to identify potential mutagenic metabolites.

Glyphosate has been extensively evaluated for its potential to induce mutations in bacteria. Most of the studies considered consist of the full battery of bacterial strains (*i.e.* the recommend strains in EPA and OECD Test Guidelines) and were evaluated at appropriate test concentrations (up to cytotoxic or assay limit concentrations).

EPA identified 27 studies that tested glyphosate technical in bacterial mutagenicity assays by means of the standard plate incorporation method or the pre-incubation modification of the standard assay. Glyphosate was negative in the presence and absence of metabolic activation in all the studies. The results of the bacterial reversion mutation assays evaluating glyphosate technical are presented in Table 5.1

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.

Test/ Endpoint	Test System	Concentrations	Purity	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA98 and TA100 and WP <i>uvrA</i> ± S9	156-5000 µg/plate	95.68%	Negative ± S9	Akanuma (1995) [MRID 50017102]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA535, TA1537, TA98 and TA100 and <i>E. coli</i> WP2P and WP2P <i>uvrA</i> ± S9	100-5000 µg/plate in DMSO	95.6% glyphosate acid	Negative ± S9	Callander (1996) [MRID 44320617]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 1535, TA1537, TA98 and TA100 and <i>E. coli</i> WP2P and WP2P <i>uvrA</i> ± S9	100-5000 µg/plate in water	60% potassium glyphosate salt	Negative ± S9	Callander (1999) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100 and TA102, ± S9	25-2000 µg in aqueous solution	Not provided	Negative ± S9	Chruscielska <i>et al.</i> (2000)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 ± S9	10-1000 µg/plate	98.4%	Negative ± S9	Flowers and Kier (1978) [MRID 00078620]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-3160 µg/plate	98.8%	Negative ± S9	Flügge (2009a) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-3160 µg/plate	96.4% technical	Negative ± S9	Flügge (2010b) ¹	

Table 5.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	Test System	Concentrations	Purity	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA98 and TA100	310-5000 µg/plate (+S9); 160-2500 µg/plate (-S9)	98.6%	Negative ± S9	Jensen (1991a) [MRID 49961502]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537 ± S9	1-1000 µg/plate	98.05%	Negative ± S9	Miyaji (2008) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538 ± S9	5000 µg/plate	Not reported	Negative ± S9	Moriya <i>et al.</i> (1983)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA97, TA98 and TA100 ± S9	33-10,000 µg/plate	99%	Negative ± S9	NTP (1992)	Hamster and rat S9
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535 and TA97a ± S9	1-5000 µg/plate	61.27 % Glyphosate isopropyl-amine salt	Negative ± S9	Ranzani (2000) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537 ± S9	648-5000 µg/plate	98.01%	Negative ± S9	Ribeiro do Val (2007) [MRID 50000903]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. Coli</i> WP2 <i>uvrA</i> ± S9	31.6-5000 µg/plate	96.0% technical	Negative ± S9	Schreib (2010) ¹	

Table 5.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	Test System	Concentrations	Purity	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98, TA100 and <i>E. coli</i> WP2 <i>hcr</i> ± S9	10-5000 µg/plate	98.4%	Negative ± S9	Shirasu <i>et al.</i> (1978) [MRID 00078619]	Published in Li & Long, 1988
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	3-5000 µg/plate (plate-incorporation), 33-5000 µg/plate (pre-incubation test)	95.1%	Negative ± S9	Sokolowski (2007a) [MRID 49957406]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	3-5000 µg/plate (plate-incorporation) 33 – 5000 µg/plate (pre-incubation test)	97.7%	Negative ± S9	Sokolowski (2007b) [MRID 49957407]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	3-5000 µg/plate (plate-incorporation) 33-5000 µg/plate (pre-incubation test)	95.0%	Negative ± S9	Sokolowski (2007c) [MRID 49957408]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	3-5000 µg/plate	96.66% technical	Negative ± S9	Sokolowski (2009a) ¹	

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.

Test/ Endpoint	Test System	Concentrations	Purity	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> pKM 101 and WP2 pKM 101 ± S9	3-5000 µg/plate	96.3% glyphosate acid	Negative ± S9	Sokolowski (2009b) [MRID 49961801]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	3-5000 µg/plate	97.16 %	Negative ± S9	Sokolowski (2010) [MRID 50000902]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538 ± S9	1-1000 µg/plate	96.0%	Negative ± S9	Suresh (1993a) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP <i>uvrA</i> ± S9	0-5000 µg/plate	95.3%	Negative ± S9	Thompson (1996) [MRID 49957409]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-5000 µg/plate	98.2%	Negative ± S9	Wallner (2010) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98 and TA100 ± S9	25 µg/plate	Not reported	Negative ± S9	Wilderman and Nazar (1982)	Rat S9 and plant cell-free homogenates were used for metabolic activation

Table 5.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	Test System	Concentrations	Purity	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98 and TA100 ± S9	0.12-10 mg/plate –S9 0.56-15 mg/plate +S9	90% glyphosate trimesium salt	Negative ± S9	Majeska <i>et al.</i> (1982a) [MRID 00126612]	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA98 and TA100 ± S9	0.005-50 µL/mL	55.6% glyphosate trimesium salt	Negative ± S9	Majeska (1985a) [MRID 00155527]	

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

5.3.2 *In vitro* Tests for Gene Mutations in Mammalian Cells

In vitro gene mutation studies in mammalian cells are conducted in cell lines with reporter genes for forward mutations. The most common reporter genes are the endogenous thymidine kinase (TK) gene, endogenous hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene and the xanthine-guanine phosphoribosyl transferase transgene (XPRT). Mutations that occur within these reporter genes result in mutant cells that are resistant to the cytotoxic effect of the pyrimidine analogue trifluorothymidine (for TK) or the purine analogue 6-thioguanine (for HPRT and XPRT) (OPPTS 870.5330). Suitable cell lines for this assay include L5178Y mouse lymphoma cells, Chinese hamster ovary (CHO) cells, hamster AS52 and V79 lung fibroblasts and human TK6 lymphoblastoid cells. Similar to other *in vitro* assays, chemicals are tested both in the presence and absence of S9 metabolic activation.

A total of four studies were conducted for (forward) mutations in mammalian cells (Table 5.3). Three studies were conducted with a high purity concentration of glyphosate technical ($\geq 95.6\%$) and the remaining study was performed with glyphosate trimesium salt. In four of the assays, mouse lymphoma L5178Y TK^{+/−} cells were the target organism and one was conducted in CHO cells with the HPRT endpoint. Glyphosate technical and the glyphosate trimesium salt were negative in the mouse lymphoma cell assays (Jensen, 1991b; Clay, 1996; Majesak, 1985b) when tested up to the current guideline limit concentration and glyphosate was negative in CHO/HPRT cells when tested up to cytotoxic concentrations (Li, 1983a).

Table 5.2. <i>In vitro</i> Mammalian Gene Mutation Assays: Glyphosate Technical.						
Test/Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y TK ^{+/−} cells ± S9	296–1000 µg/mL	95.6%	Negative	Clay (1996) ¹	Relative survival was 90% (-S9) and 57% (+S9) at top concentration
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y TK ^{+/−} cells ± S9	520–4200 µg/mL (+S9); 610–5000 µg/mL (-S9)	98.6%	Negative	Jensen (1991b) [MRID 49961504]	Reported no significant reduction in cloning efficiency at any concentration.
Gene Mutations in Mammalian Cells	Chinese hamster ovary (CHO) cells, HPRT locus ± S9	500–25000 µg/mL (+S9); 500–22500 µg/mL (-S9)	98.7%	Negative	Li (1983a); [MRID 00132681]	Tested S9 from 1–10% Cytotoxic at 22.5 mg/mL (-S9, and with 1,2 and 10% S9) and at 17.5 mg/ml (10% S9)
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y TK ^{+/−} cells ± S9	1–5 µl/mL	55.6% <i>Glyphosate trimesium salt</i>	Negative	Majeska (1985b) [MRID 00155530]	Negative with pH adjusted

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

5.4 *In vitro* Tests for Chromosomal Abnormalities

Cytogenetic assays are tests that can detect chemicals that cause structural chromosomal damage (clastogenicity) or affect the segregation of chromosomes during cell division and alter chromosome number (aneuploidy). Generally, there are two types of *in vitro* cytogenetic assays that identify chemicals inducing chromosomal abnormalities: chromosomal aberration assays and micronucleus assays. Although chromosomal damage observed in these assays are not considered heritable mutations, chemicals that can induce these types of chromosomal damage can also induce transmissible mutations to daughter cells indicating their role in cancer (Yauk *et al.*, 2015; OECD 2015). In addition, assays such as (fluorescence *in situ* hybridization (FISH)) can provide additional mechanistic information on the formation of chromosomal abnormalities. It is important to note that factors such as cytotoxicity, solubility of the test substance, changes in pH or osmolality play a significant role in the outcome of the assay. Like other *in vitro* assays, compounds are generally tested in the presence or absence of S9 metabolic activation to determine if metabolism affects the genotoxic activity of the parent compound and to determine if potential genotoxic metabolites are formed.

5.4.1 *In vitro* Mammalian Chromosomal Aberration Test

Chromosomal aberration assays detect both structural chromosomal and numerical aberrations. Structural chromosomal aberrations are of two types: chromatid and chromosome and include breaks, deletions and rearrangements (OPPTS 870.5375, OECD 2015). Numerical chromosomal aberrations generally result from the loss of an entire chromosome mostly due to damage in the spindle fiber resulting in aneuploidy. The types of cells that are most commonly used in chromosomal aberration assays include established cell lines such as Chinese hamster lung (CHL) and CHO cells or primary cell cultures such as human or other mammalian peripheral blood lymphocytes. In this assay, cells are typically sampled at a time equivalent to the length of approximately 1.5 cell cycles from the start of treatment. Prior to harvesting, cells are treated with Colcemid® or colchicine to arrest cells at the first metaphase stage of the cell cycle following the beginning of exposure to the test article. Once harvested, the cells are stained and metaphase cells are evaluated microscopically for various types of chromosome aberrations. (OECD TG 473). Data should be presented in a way that indicates the percentage of affected cells in the population of cells scored (e.g., % cells with aberrations or # aberrant cells/100 cells). Gaps should not be included in the analysis; they are scored but gaps alone in the absence of any additional chromosomal aberrations (e.g., a fragment or a ring chromosome) are not sufficient to define a cell as aberrant.

Glyphosate technical was evaluated in eight chromosomal aberrations tests to determine its potential to induce clastogenic effects *in vitro*. The findings are presented in Table 5.3. Six of the eight studies were negative. The two positive studies were both from the same laboratory where, Lioi *et al.* reported an increase in chromosomal aberrations at glyphosate concentrations of 8.5 µM and above in bovine lymphocytes (Lioi *et al.*, 1998b) and at all concentrations of glyphosate tested (7-170 µM) in human lymphocytes (Lioi *et al.*, 1998a) following a 72-hour exposure period. No chromosomal aberrations were observed as a result of exposure to glyphosate in one study using CHO cells (Majeska, 1985c) and in two studies with CHL cells

(Matsumoto, 1995; and Wright, 1996). Sivikova and Dianovsky (2006) reported no statistically significant increases in chromosomal aberrations in bovine lymphocytes treated with glyphosate (62% pure) at concentrations up to 1120 μ M following 24-hour exposure. (Sivikova and Dianovsky, 2006). In studies conducted with human lymphocytes treated with glyphosate ($\geq 95\%$) for 24-96 hours at concentrations, no increase in chromosomal aberrations were seen at concentrations as high as 6000 μ M (Fox, 1998; and Manas *et al.*, 2009).

5.4.2 *In vitro* Mammalian Micronucleus Test

The *in vitro* micronucleus test can detect the induction of micronuclei in the cytoplasm of cells in the interphase stage of the cell cycle. Micronuclei form from acentric chromosome fragments (i.e., chromosome fragments lacking a centromere) or when whole chromosomes are unable to migrate to the cellular poles during anaphase prior to cell division. (OECD 487). Thus, the micronucleus assay can detect both structural and numerical chromosomal changes. It should be noted, however, that additional work is required to distinguish whether induced micronuclei have arisen from a clastogenic versus an aneugenic mechanism, *e.g.*, staining micronuclei to detect the presence of kinetochore proteins. The assay is typically performed with cell lines or primary cell cultures of human or rodent origin. The assay can be conducted with the addition of cytochalasin B which inhibits cytokinesis resulting in the formation of binucleated cells. The presence of binucleated cells, indicates that cells have undergone one round of mitosis, a necessary prerequisite for micronucleus formation.

Six studies evaluated glyphosate technical for its potential to induce micronuclei *in vitro* (Table 5.4). Four of the six studies were positive and the remaining two studies were equivocal. In a study by Koller *et al.* (2012), TR146 cells (derived from a human neck metastasis of buccal epithelial origin) were treated for 20 minutes with up to 20 mg/L (~ 0.12 mM) glyphosate (95%), the authors reported a statistically significant increase in binucleated cells with micronuclei at 15 (~ 0.09 mM) and 20 (~ 0.12 mM) mg/L, and also indicated significant apoptosis and necrosis at 20 mg/L. The short exposure period in this study was unusually short (20 minutes) and was conducted in a tumor cell line that had not been well characterized in regards to its degree of chromosomal instability and DNA damage and repair capacity. In another study, Roustan *et al.* (2014) reported positive findings +S9 only in CHO cells treated with glyphosate (unknown purity) at 10- 100 μ g/mL with little evidence of a dose response over that concentration range.

Two other studies evaluated glyphosate technical in human lymphocytes (Mladinic *et al.*, 2009a, 2009b). These studies used an exposure protocol that is different from the OECD recommendations for the *in vitro* micronucleus assay. OECD recommends that whole blood or isolated lymphocytes are cultured in the presence of a mitogen (*e.g.* phytohemagglutinin; PHA) prior to exposure of a test chemical in order to detect micronuclei formed via an aneugenic mechanism. However, in these two studies, blood cells were exposed to glyphosate for 4 hours, washed, and then treated with PHA to stimulate cell division. Both studies reported a statistically significant increase in micronucleated cells at 580 μ g/mL (~ 3.4 mM), but not at lower concentrations, following 4-hour exposures in the presence of S9. The frequency of micronucleated cells (+S9) ranged from 11.3 to 28.7 in one study (Mladinic *et al.*, 2009a) and 33.3 to 65.2 in the other study (Mladinic *et al.*, 2009b) over the 1000-fold concentration range. No statistically significant increases in micronucleated cells were seen in either study in the absence of S9 activation. When cells were evaluated with vital stains, cells treated with 580

µg/mL showed a significant ($p < 0.05$) increase in the percentage of cells undergoing apoptosis and necrosis compared to the negative controls.

Piesova *et al.* (2004, 2005) conducted two *in vitro* micronucleus studies using glyphosate technical (62%) up to 560 µM in bovine lymphocytes. In the 2004 study, bovine lymphocytes from two donors were treated for 24 or 48 hours without S9 metabolic activation, and for 2 hours (with and without S9 activation) or 48 hours (-S9) in the 2005 study. Both studies yielded similar results following 48-hour exposure to glyphosate. In both cases, the authors reported a weak induction of micronuclei in one donor at 280 µM and at 560 µM in the second donor. The induction was approximately 2-fold ($p < 0.05$), but with no clear dose response. No effects on micronuclei induction were seen at the 2- or 24-hour time points; however, with these early time points it is unlikely that one cell division has occurred during or after treatment.

Table 5.3. <i>In vitro</i> Tests for Chromosome Aberrations in Mammalian Cells- Glyphosate Technical						
Test/Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
<i>In vitro</i> Chromosomal Aberration	Chinese hamster ovary (CHO) cells	4-10 µl/mL, ± S9	55.6% <i>Glyphosate trimesium salt</i>	Negative	Majeska (1985c) [MRID 00155530]	pH adjusted (7.4-7.6)
<i>In vitro</i> Chromosomal Aberration	Chinese Hamster lung (CHL) cells	±S9: 0, 250, 500, 1000 and 2000 µg/mL; 24 and 48 h treatment - S9; 6 h treatment ±S9 harvest 24 h	95.68%	Negative	Matsumoto (1995) [MRID 50017106]	Decline in pH noted at 500 and 1000 µg/mL.
<i>In vitro</i> Chromosomal Aberration	Chinese hamster lung (CHL) cells	-S9: 24 & 48-hr exposure: 0-1250 µg/mL; +S9: 0-1250 µg/mL	95.3%	Negative	Wright (1996) [MRID 49957410]	Excessive decrease in pH >1250 µg/mL
<i>In vitro</i> Chromosomal Aberration	Bovine lymphocytes	-S9 only: 0, 7, 85 and 170 µM; 72 h exposure	≥98%	Positive (all concs.)	Lioi <i>et al.</i> (1998b)	
<i>In vitro</i> Chromosomal Aberration	Bovine lymphocytes	±S9: 0, 28, 56, 140, 280, 560 and 1120 µM; 24 h exposure	62.0%	Negative	Sivikova and Dianovsky (2006)	Decreased MI and PI at ≥ 560 µM
<i>In vitro</i> Chromosomal Aberration	Human lymphocytes	±S9: 100-1250 µg/mL cultures analyzed; 68 & 92 h	95.6%	Negative	Fox (1998) [MRID 49961803]	Excessive decrease in pH >1250 µg/mL
<i>In vitro</i> Chromosomal Aberration	Human lymphocytes	-S9 only: 0, 5.0, 8.5, 17.0 and 51.1 µM; 72 h exposure	≥98%	Positive ≥ 8.5 µM	Lioi <i>et al.</i> (1998a)	No significant ↓ in MI observed.
<i>In vitro</i> Chromosomal Aberration	Human lymphocytes	-S9: 0, 200, 1200 and 6000 µM; 48 h exposure	96.0%	Negative	Manas <i>et al.</i> (2009)	No toxicity observed up to 6000 µM

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

CA= chromosomal aberrations, MI= mitotic index, PI= proliferation index.

Table 5.4. <i>In vitro</i> Tests for Micronuclei Induction in Mammalian Cells- Glyphosate Technical						
Test/ Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
<i>In vitro</i> Cytokinesis Block Micronucleus Assay (with FISH analysis)	TR146 cells (human-derived buccal carcinoma cell line)	10, 15 and 20 mg/L; 20-minute exposure.	95%	Positive Statistically significant ($p < 0.05$) increase in MN at 15 and 20 mg/L.	Koller <i>et al.</i> (2012)	Apoptosis and necrosis reported at 20 mg/L Also reported ↑ in NB and NPB
<i>In vitro</i> Cytokinesis Block Micronucleus Test	CHO-K1 cells	5 - 100 µg/mL, ±S9	Not stated	Negative –S9 Positive +S9 at 10-100 µg/mL	Roustan <i>et al.</i> , (2014)	No clear dose response
<i>In vitro</i> Cytokinesis Block Micronucleus Test	Bovine lymphocytes (2 donors)	0, 28, 56, 140, 280 and 560 µM 24 & 48 h exposure	62%	24 h: Negative 48 h: Equivocal ↑ MN at 280 µM only (donor A) ↑ MN at 560 µM only (donor B)	Piesova, 2004	No dose-response No significant decrease in CBPI observed.
<i>In vitro</i> Cytokinesis Block Micronucleus Test	Bovine lymphocytes (2 donors)	0, 28, 56, 140, 280 and 560 µM; 2 h (±S9) and 48 h (-S9) exposure	62%	2 h: Negative 48 h: Equivocal ↑ MN at 280 µM only (donor A) and at 560 µM only (donor B)	Piesova, 2005	No dose-response; No significant decrease in CBPI observed. Metabolic activation had no effect on MN formation after 2 h exposure.

Table 5.4. <i>In vitro</i> Tests for Micronuclei Induction in Mammalian Cells- Glyphosate Technical						
Test/ Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
<i>In vitro</i> Cytokinesis Block Micronucleus Assay (with FISH analysis)	Human lymphocytes (treated with cytochalasin B)	4h treatment $\pm$ S9; 0.5, 2.91, 3.50, 92.8 and 580 μ g/mL; harvested 72 h	98.0%	Negative –S9 Positive +S9, $\uparrow$ MN at 580 μ g/mL, but not at 0.5-92.8 μ g/mL Also observed $\uparrow$ in NB at 580 μ g/mL ($\pm$ S9); $\uparrow$ NPB at 580 μ g/mL (+S9)	Mladinic <i>et al.</i> (2009a)	Cells were exposed to glyphosate and washed prior to treatment with PHA. Authors did not report being blind to treatment.
<i>In vitro</i> Cytokinesis Block Micronucleus Assay (with FISH analysis)	Human lymphocytes (treated with cytochalasin B)	4h treatment $\pm$ S9; 0.5, 2.91, 3.50, 92.8 and 580 μ g/mL	98%	Negative –S9 Positive +S9 $\uparrow$ MN at 580 μ g/mL, but not at 0.5 -92.8 μ g/mL $\uparrow$ apoptosis and necrosis at 580 μ g/mL (-S9); $\uparrow$ apoptosis at $\geq$ 2.91 μ g/mL and necrosis at 580 μ g/mL (+S9) $\uparrow$ in NB at 580 μ g/mL ($\pm$ S9) and NPB at 580 μ g/mL (+S9)	Mladinic <i>et al.</i> (2009b)	Cells were exposed to glyphosate and washed prior to treatment with PHA. Authors did not report being blind to treatment. .

CBPI= cytokinesis block proliferation index, FISH= fluorescent in situ hybridization; MN= micronuclei; NB= nuclear buds; NPB= nucleoplasmic bridges.

5.5 In Vivo Genetic Toxicology Tests

5.5.1 In Vivo Assays for Chromosomal Abnormalities

5.5.1.1 Mammalian Bone Marrow Chromosomal Aberration Assays

The *in vivo* mammalian bone marrow chromosomal assay detects the ability of a chemical to cause structural chromosomal damage in cells in the bone marrow. The assay is typically conducted in rodents (mouse or rat) and detects both chromosome-type and chromatid-type aberrations. Chromatid-type aberrations are expressed when a single chromatid break occurs and/or a reunion between chromatids, and chromosome-type aberrations result from damage expressed in both sister chromatids (OPPTS 870.5385). In this test, animals are exposed (typically via oral route or intraperitoneal injection) and sacrificed at sequential intervals. Prior to sacrifice, animals are treated with a spindle inhibitor such as colchicine or Colcemid® to arrest cells at metaphase. Chromosome preparations from the bone marrow are stained and scored for chromosomal aberrations. (OPPTS 870.5385). Generally, the optimal time to detect chromosomal aberrations in the bone marrow is 24 hours after treatment.

Three *in vivo* mammalian bone marrow chromosomal assays were conducted with glyphosate technical for regulatory purposes and all were negative (Table 5.8). In the first study, Sprague Dawley rats were administered glyphosate (98%) at 0 or 1000 mg/kg and the bone marrow was sampled at 6, 12 or 24 hours after dosing. No significant increase in bone marrow chromosomal aberrations were observed (Li, 1983b). In the second study, Swiss albino mice were treated twice by oral gavage (24 hours apart) with 0 or 5000 mg/kg glyphosate technical (96.8%) resulting in no significant increase in bone marrow chromosomal aberrations (Suresh, 1994). In a third study conducted with glyphosate trimesium salt, no increase in chromosomal aberrations were seen in the bone marrow of rats treated by oral gavage with up to 188 mg/kg (Majeska, 1982c).

5.5.1.2 Rodent Dominant Lethal Test

Dominant lethal mutations cause embryonic or fetal death. The induction of a dominant lethal mutation after exposure to a chemical indicates that the test chemical has affected the germinal tissue (sperm at some point in development, from stem cell to spermatocyte). Dominant lethal effects are considered to result from chromosomal damage (structural or numerical), but may also reflect gene mutations or systemic toxicity (OPPTS 870.5450, OECD 2016). In this test, male rodents are treated with the test material and mated with (untreated) virgin females. The female animals are sacrificed at an appropriate time and the uteri are examined to determine the number of implants, and live and dead embryos. Two dominant lethal studies were identified. One study was conducted in the rat (Suresh, 1992) where male rats were dosed by oral gavage with glyphosate up to 5000 mg/kg. The other study (Rodney, 1980) was conducted in male mice treated with up to 2000 mg/kg glyphosate (98.7%) by oral gavage. No significant increase in dominant lethal mutations were observed in either study (Table 5.5).

5.5.1.3 *In Vivo* Mammalian Erythrocyte Micronucleus Assays

The mammalian micronucleus test is the most commonly conducted *in vivo* test to detect clastogenic or aneugenic chemicals. The test identifies chemicals that induce micronuclei in proerythrocytes (progenitor cells) by assessing micronucleus frequency in immature erythrocytes (polychromatic erythrocytes, PCEs) sampled from the bone marrow or from the peripheral blood (reticulocytes). This test is typically conducted in mice or rats. When bone marrow erythroblasts develop into erythrocytes, the main nucleus is extruded following the final cell division (erythrocytes are the only mammalian cell that does not contain a nucleus). Any micronuclei formed after the final cell division may remain in the cytoplasm following extrusion of the main nucleus. The visualization of micronuclei is facilitated by the lack of a nucleus in these cells (OPPTS 870.5395, OECD 474). Micronuclei can originate from acentric chromosomes, lagging chromosome fragments, or whole chromosomes; thus, micronuclei are biomarkers of both altered chromosome structure or chromosome number. The assay is based on an increase in the frequency of micronucleated erythrocytes in treated animals, in either peripheral blood samples or bone marrow samples (OPPTS 870.5395). Additional mechanistic information on the formation of chromosomal abnormalities can be obtained from the incorporation of centromeric and telomeric fluorescent probes (FISH) assay. According to EPA test guidelines, a single dose of the test substance may be used in this test if the dose is the maximum tolerated dose (MTD), a dose that produces some indication of bone marrow cytotoxicity (e.g., a reduction in the proportion of immature erythrocytes (PCEs) to total erythrocytes by >50%) or a maximum limit dose of 5000 mg/kg. The routes of administration for this test are typically oral or intraperitoneal injection and generally involve a single administration.

Glyphosate technical has been extensively evaluated for micronuclei induction in *in vivo* studies. Fourteen studies were conducted for regulatory purposes, four were identified from the open literature, and one study was conducted by the U.S. National Toxicology Program (NTP). This included nine studies with administration of glyphosate by the intraperitoneal (i.p.) route and 10 studies by the oral route. The findings are presented in Table 5.10. Of the nine i.p. studies, seven (Costa, 2008; Chruscielska *et al.*, 2000; Durward, 2006; Gava, 2000; Marques, 1999; Rank *et al.*, 1993 and Zaccaria, 1996) were negative. These studies tested doses as high as 2016 mg/kg (single and double administration) with sampling times at 24- and 48-hours post-dose. Two positive findings were reported when glyphosate technical was administered by i.p. Bolognesi *et al.* (1997) reported a significant increase in micronuclei in the bone marrow of male Swiss CD mice 24 hours after i.p. treatment with 300 mg/kg glyphosate technical (99.9%). The dose in this study was administered as ½ dose (150 mg/kg) injections 24 hours apart to 3 male mice. Manas *et al.* (2009) evaluated glyphosate technical (96%) in BALB/c male and female mice (5/sex/dose) administered 50, 100 or 200 mg/kg by two i.p. injections, 24 hours apart. The results showed a significant increase in micronucleated erythrocytes at 200 mg/kg, but not at 50 or 100 mg/kg. It should be noted that doses that resulted in the positive responses in these two studies were above the reported i.p. LD50 value (130 mg/kg) for glyphosate in mice (NTP 1992).

Glyphosate technical was also evaluated in nine micronucleus assays with administration by the oral route in mice and one in the rat. Eight of the nine oral studies in the mouse were negative for micronuclei induction. The single positive response was seen in female mice treated with

two 5000 mg/kg doses (limit dose), 24 hours apart with bone marrow sampling at 24-hours post-dose (Suresh, 1993b). No increase was observed at lower doses (50 and 500 mg/kg) in females or at any dose in males. The eight negative oral studies in mice included single dose administrations of 5000 mg/kg and bone marrow analysis at 24, 48, and/or 72 hours (Jensen, 1991c; Fox and Mackay, 1996) and one or two administrations of glyphosate technical with top doses between 30 and 2000 mg/kg (Honarvar, 2005; Honarvar, 2008; Jones, 1999; and Zoriki-Hosmi, 2007). It should be noted that evaluations at 48 and 72 hours post dose may be too late to detect chemically-induced micronucleated PCEs in the bone marrow as these cells may have already migrated into the peripheral blood. No significant increase in micronucleated erythrocytes were seen in male or female mice following 13-weeks of dietary (feed) administration of glyphosate technical at doses up to 3393 mg/kg/day (NTP, 1992). In the single study that evaluated micronuclei induction in rats, glyphosate technical did not induce significant induce micronuclei in CD1 rats treated by oral gavage at doses up to 2000 mg/kg (Flügge, 2009b). When glyphosate trimesium salt was evaluated, no increase in micronuclei induction was seen in mice treated orally up to 1100 and 800 mg/kg in males and females, respectively (Majeska, 1987).

Table 5.5. <i>In Vivo</i> Tests for Chromosomal Aberrations in Mammals- Glyphosate Technical.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Chromosomal Aberration Test	Sprague Dawley rats (males and females)	Intraperitoneal injection; sampled at 6, 12 and 24 h after treatment	0, 1000 mg/kg (6/sex/dose/sampling time)	98%	Negative	Li (1983b) [MRID 00132683]	No toxicity observed. A separate study using ¹⁴ C-glyphosate showed that glyphosate reaches BM 0.5 h after dosing with ½ life elimination at 7.6 h. Peak BM value was 400 ppm, corresponding to 2000 ppm plasma value.
Bone Marrow Chromosomal Aberration Test	Sprague Dawley rats (males and females) Vehicle: distilled water	Oral gavage, sampling after 6, 12, 24, 48 h and 5 d	0, 21, 63 and 188 mg/kg	58.5% <i>Glyphosate trimesium salt</i>	Negative	Majeska (1982c) [MRID 00132176]	
Bone Marrow Chromosomal Aberration Test	Swiss Albino mice (males and females) Vehicle: peanut oil	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 5000 mg/kg (5/sex/dose)	96.8%	Negative	Suresh (1994) [MRID 49987408]	Significant (p<0.05) decrease in bw of females at high dose.
Rodent Dominant Lethal Test	CD-1 mice Each dosed male mated with 2 females/week for 8 weeks	Oral gavage	0, 200, 800, and 2000 mg/kg	98.7%	Negative	Rodwell (1980) [MRID 00046364]	
Rodent Dominant Lethal Test	Wistar rat Each dosed male mated with 1 female/week for 10 weeks	Oral gavage	0, 200, 100 and 5000 mg/kg	96.8%	Negative	Suresh (1992) [MRID 49987404]	

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss CD1 mice (males only)	Intraperitoneal injection; 2 injections of half the dosage of 300 mg/kg 24 h apart; sampling at 6 and 24 h	0, 300 mg/kg (3/dose)	99.9%	Positive Stat significant increase in MN at 24 h	Bolognesi <i>et al.</i> (1997)	Material and methods indicate 3 animals/dose; however, Table 1 of article indicates 4 animals were evaluated.
Bone Marrow Micronucleus Test	Balb C mice (males and females) Vehicle: Saline	Intraperitoneal Injection (two injections, 24 h apart); sampling after 24 h (last treatment)	0, 50, 100, and 200 mg/kg (5/sex/dose)	96%	Positive ↑MN at 200 mg/kg, but not at 50 or 100 mg/kg	Manas <i>et al.</i> (2009)	No significant signs of toxicity observed.
Bone Marrow Micronucleus Test	C3H mice (males only) Vehicle: water	Intraperitoneal Injection (single treatment); sampling after 24, 48 and 72 h	0, 300 mg/kg	Not reported	Negative	Chruscielska <i>et al.</i> (2000)	
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: corn oil	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 15.62, 31.25, and 62.5 mg/kg (5/sex/dose)	980 g/kg Glyphosate technical	Negative#	Costa (2008) ¹	OECD guideline 474 #Was not tested up to limit dose and did not demonstrate that compound was tested up to toxic dose. No mention of BM toxicity or clinical signs.

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Crl:CD-1TM(ICR) BR mice (males only ¹) Vehicle: PBS	Intraperitoneal Injection (single treatment); sampling after 24 and 48 h (high dose only)	0, 150, 300 and 600 mg/kg (7/dose)	95.7%	Negative	Durward (2006) [MRID 49957411]	Clinical signs reported at ≥ 150 mg/kg. Significant $\downarrow$ in %PCEs reported at 24 h in 600 mg/kg group. $\uparrow$ in MN PCEs observed at 600 mg/kg (1.9 ± 0.7 vs. 1.0 ± 1.2 control; $p < 0.05$), at 24 h, but not 48 h, within historical control range.
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 1008, 2016, and 3024 mg/kg 5/sex/dose	612.7 g/kg (glyphosate technical Nufarm)	Negative	Gava (2000) ¹	LD50 was 4032 mg/kg Mortality observed in 1 animal at high dose (only 4 m/f scored for MPCEs). No effect on PCE/NCE.
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 187.5, 375 and 562.5 mg/kg 5/sex/dose	954.9 g/kg (glyphosate technical Nufarm)	Negative	Marques (1999) [MRID 49957412]	LD50 was 750 mg/kg No significant signs of toxicity observed in main study
Bone Marrow Micronucleus Test	NMRI-Bom mice	Intraperitoneal Injection (single treatment); sampling after 24 h (all doses) and 48 h (150 and 200 mg/kg)	0, 150, and 200 mg/kg (5/sex/dose)	glyphosate isopropyla mine (purity not specified)	Negative	Rank <i>et al.</i> (1993)	

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss albino mice (males and females)	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 68, 137, and 206 mg/kg (	360 g/L	Negative	Zaccaria (1996) [MRID 49961501]	Doses selected were reported as corresponding to 25, 50 and 75% LD ₅₀
Bone Marrow Micronucleus Test	CD-1 mice (males and females) Vehicle: saline	Oral gavage (single treatment); sampling after 24 and 48 h	0, 5000 mg/kg 5/sex/dose	95.6%	Negative	Fox and Mackay (1996) [MRID 44320619]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: PEG 400	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg 5 sex/dose	97.73%	Negative	Honarvar (2005) ¹	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males only) Vehicle: 0.5% carboxymethyl-cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/dose)	99.1%	Negative	Honarvar (2008) [MRID 49961802]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: 0.5% carboxymethyl-cellulose	Oral gavage (single treatment); sampling after 24, 48 and 72h	0, 5000 mg/kg; 5/sex/dose	98.6%	Negative	Jensen (1991c) [MRID 49961503]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	CD-1 mice (males only ¹) Vehicle: water	Oral gavage single treatment); sampling after 24 and 48 h	0, 2000 mg/kg 5/dose	59.3% potassium glyphosate salt	Negative	Jones (1999) ¹	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	Swiss albino mice; (males and females) Vehicle: peanut oil	Oral gavage (2 treatments, 24 h apart); sampling	0, 50, 500, 5000 mg/kg 5/sex/dose	96.8% glyphosate acid	Positive in females at 5000	Suresh (1993b) [MRID 49987407]	No significant signs of toxicity observed

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
		after 24 h (last treatment)			mg/kg only. Negative in males at all doses		
Bone Marrow Micronucleus Test	Swiss mice (males only) Vehicle: corn oil	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 8, 15 and 30 mg/kg (6/dose)	980.1 g/kg	Negative	Zoriki Hosomi (2007) [MRID 50000901]	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	CD-1 mice (males and females) Vehicle: distilled water	Oral gavage, Sampling 24, 48 and 72 h after treatment	Males: 0, 700, 900 and 1100 mg/kg Females: 0, 400, 600 and 800 mg/kg	55.3% <i>Glyphosate trimesium salt</i>	Negative	Majeska (1987) [MRID 40214004]	
Bone Marrow Micronucleus Test	B6CF3 Mice (males and females)	Oral (dietary). MN assay conducted following 13-week feed study.	0, 205/213, 410/421, 811/844, 1678/1690 and 3393/3393 mg/kg (m/f) (10/sex/dose)	99%	Negative	NTP (1992)	
Bone Marrow Micronucleus Test	CD Rats (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	98.8%	Negative	Flügge (2009b) ¹	OECD guideline 474 No significant signs of toxicity observed

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline followed, test material purity, control chemicals and summary data tables.

² Only males tested; report indicated that there was no difference between sexes seen in range finding study.

CA= chromosomal aberrations, MPCE= micronucleated polychromatic erythrocytes, NCE= normochromatic erythrocytes, PCE=polychromatic erythrocytes.

5.6 Additional Genotoxicity Assays Evaluating Primary DNA Damage

There are a number of genotoxicity assays that evaluate primary DNA damage, but do not measure the consequence of the genetic damage (*i.e.*, mutation or chromosomal damage). As discussed in the Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines (OECD 2015), the endpoints measured in primary DNA damage tests such as DNA adducts, comet assay, or unscheduled DNA synthesis may lead to cell death or may initiate DNA repair, rather than a mutation. These types of assays can, however, provide mechanistic information when interpreting positive findings in other genotoxicity tests or when determining whether a chemical is acting through a mutagenic mode of action. Additionally, indirect mechanisms of DNA damage such as oxidative DNA damage can be detected by these test systems. Oxidative damage results from oxidative stress, which occurs when there is a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant defense systems. Normal cellular metabolism is a source of endogenous reactive oxygen species that accounts for background levels of oxidative damage in normal cells. Some types of oxidative damage are repairable while others lead to serious consequences in the cell. (Cooke *et al.*, 2003). The various assays evaluating primary DNA damage in glyphosate technical are presented in Table 5.7. Details of the findings are discussed below.

Glyphosate technical is not electrophilic and is not considered to be DNA-reactive. In a study to evaluate the potential for glyphosate to directly interact with DNA, Peluso *et al.* (1998) reported that glyphosate technical did not form DNA adducts in mice when tested up to 270 mg/kg via i.p. Bolognesi *et al.* (1997) reported an increase in the oxidative damage biomarker 8-hydroxydeoxyguanosine (8-OHdG) in the liver 24 h after i.p. injection of 300 mg/kg in mice. No increase in 8-OHdG was seen in the kidney with glyphosate technical. The dose in this study was high (300 mg/kg) for an i.p. injection and within the i.p. LD₅₀ range (134- 545 mg/kg) that has been reported elsewhere (WHO, 1994).

The comet assay, also known as single cell gel electrophoresis (SCGE), is a sensitive and rapid method to detect DNA strand breaks in individual cells. In this assay, individual cells are embedded in agarose. The cells are then lysed (which digests the cellular and nuclear membranes) and the DNA is allowed to unwind under alkaline or neutral conditions. During electrophoresis, chromatin (which is in a supercoiled state) that has undergone steric relaxation due to DNA damage migrates away from the nucleoid (nucleus) toward the anode, yielding images that resemble a comet. The intensity of the comet tail relative to the comet head reflects the amount of DNA breakage (Tice *et al.*, 2000; Collins *et al.*, 2008). The comet assay can detect single and double strand breaks resulting from direct interactions with DNA, alkali labile sites, or transient DNA breaks resulting during DNA excision repair. These types of strand breaks may be, (a) repaired with no persistent effect, (b) be lethal to the cell or (c) be fixed as a mutation (OECD TG 489). DNA strand breaks in the comet assay can be measured by endpoints such as percent tail DNA (also referred to as % tail intensity), tail length, and tail moment. However, % tail DNA is the recommended metric for evaluating and interpreting results using this assay (OECD TG 489).

The five studies that evaluated glyphosate technical using the comet assay are summarized in Table 5.12. Two of the studies were conducted using tumor cell lines. Koller *et al.* (2012) reported positive comet effects (increased tail intensity) in a human buccal carcinoma cell line (TR146) following a 20-minute treatment with ≥ 20 mg/L (~ 0.118 mM) glyphosate. Although no evidence of cytotoxicity was reported in this study, the authors did report an increase in apoptosis and necrosis at the same concentrations (≥ 20 mg/L) when the same cell line was tested for *in vitro* micronuclei induction (discussed previously). In a study using Hep-2 cells (presumably a HeLa cell derivative), Manas *et al.* (2009) reported a statistically significant increase in mean tail length, and tail intensity at all concentrations (3.0-7.5 mM) tested. In a comet study conducted on human lymphocytes, Alvarez-Moya *et al.* (2014) reported significant increases in tail length only (but not % tail DNA) following treatment with glyphosate concentrations of 0.7-700 μ M. Mladinic *et al.* (2009a) evaluated DNA damage in non-dividing human lymphocytes ($\pm$ S9) following treatment from 0.5 to 580 μ g/mL using the standard alkaline comet method and a modified comet method that detects DNA damage due to oxidative damage (human 8-hydroxyguanine DNA-glycosylase, hOGG1 comet method). In this study, the authors reported statistically significant increases in tail intensity at 3.5 μ g/mL and higher in the absence of S9, with significance only at 580 μ g/mL (~ 3.4 mM) in the presence of S9 using the alkaline method. This concentration also resulted in increased apoptosis and necrosis as well as an increase in plasma total antioxidant capacity (TAC) and changes in plasma lipid peroxidation (thiobarbituric reactive substances, TBARs); however, only a dose-related increase in tail length (not % tail DNA) was observed at 580 μ g/mL (+S9) using the hOGG1 method. When the Manas *et al.* (2013) evaluated blood and liver cells following a 14-day drinking water study in mice treated with 40 and 400 mg/kg/day glyphosate, significant increases in tail intensity, tail length and tail moment were reported were observed at both doses in both tissues (except for DNA tail intensity in liver at 40 mg/kg); however, there were no substantial effects on oxidative stress measurements suggesting that DNA damage reported may not be due to oxidative damage.

The Unscheduled DNA Synthesis (UDS) test with mammalian liver cells *in vitro* identifies substances that induce DNA repair after excision and removal of a segment of damaged DNA. The test is typically conducted in liver cells, which have relatively few cells in the S-phase of the cell cycle. The assay measures the incorporation of radiolabeled nucleotide [^{3} H]-thymidine into DNA during the repair process in non-S phase cells. (OPPTS 870.5555). Substances that produce either a statistically significant dose-related increase or statistically significant and reproducible increase in ^{3} H-TdR incorporation in at least one test point are considered to be positive in this test. A UDS study that evaluated glyphosate technical in rat primary hepatocytes was negative (Williams, 1978). Glyphosate technical was also negative in a DNA repair test conducted in bacteria (Rec-A test) (Shirasu, 1978).

In an alkaline elution assay, which detects single strand DNA breaks, Bolognesi *et al.* (1997) reported an increase in single strand breaks (i.e. increased DNA elution rate) in the liver and kidney 4 hours after a single i.p. injection of 300 mg/kg. The elution rate returned to control levels at 24 hours. Glyphosate technical was also negative in a DNA repair test conducted in *Bacillus subtilis* H17 (rec⁺) and M45 (rec⁻) bacterial Rec-A test (Shirasu, 1978).

Finally, the sister chromatid exchange (SCE) test is an assay that can measure the consequence of primary DNA damage. The mechanism(s) of action for chemical induction of SCE is unclear. The SCE assay detects the exchange of DNA between two sister chromatid arms within a single chromosome. The assay can be performed *in vitro* or *in vivo*. Following exposure, cells/animals are treated with bromodeoxyuridine (BrdU) to allow for the differentiation of the two sister chromatids (harlequin staining) and prior to harvest are treated with a spindle inhibitor to accumulate cells in metaphase. The chromosome preparations are then stained and analyzed for SCEs (OPPTS 870.5900, 870.5915). The SCE studies that evaluated glyphosate technical are also presented in Table 12. Positive SCE findings were reported in all four studies; two evaluating bovine lymphocytes (Lioi, 1988b, Sivikova and Dianovksy, 2006) and two studies evaluating human lymphocytes (Lioi, 1988a; Bolognesi *et al.*, 1997). In all four studies the induction did not demonstrate a clear dose response.

Additionally, although it is recognized that mechanisms other than genotoxicity may be involved in cell transformation, glyphosate trimesium salt was evaluated in the Balb/3T cell transformation assay (an *in vitro* tumor formation assay) and was negative up to 5.0 mg/ml (Majeska, 1982b).

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.							
Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
DNA Adducts ³² P-postlabeling	Swiss CD1 mice (males and females) Liver and kidney evaluated	Intraperitoneal injection; 24 h exposure	0, 130 and 270 mg/kg	Not reported	Negative	Peluso <i>et al.</i> (1998)	
DNA oxidative damage: 8-OHdG formation	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	0, 300 mg/kg (3/dose)	99.9%	Kidney: negative Liver: positive (24 h)	Bolognesi <i>et al.</i> (1997)	
Single-cell gel electrophoresis (SCGE) assays- Comet assay	TR146 cells (human-derived buccal epithelial cell line).	NA (<i>in vitro</i>)	-S9: 10-2000 mg/L; 20-minute exposure.	95%	Positive Increased DNA migration at >20 mg/L	Koller <i>et al.</i> (2012)	Also measured multiple cellular integrity parameters to assess cytotoxicity. No clear evidence of cytotoxicity seen except for increase in enzyme activity (indicative of membrane damage) in LDHe (extracellular lactate dehydrogenase) assay at >80 mg/L. No mention of monitoring pH
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Hep-2 cells	NA (<i>in vitro</i>)	0, 3, 4.5, 6, 7.5, 9, 12 and 15 mM	96%	Positive Stat. significant increase in mean tail length, and tail intensity at all concs.	Manas <i>et al.</i> (2009)	The authors did not report a source for the Hep-2 cells. The agency presumes that this is a HeLa derived cervical carcinoma cell line.

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.							
Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Human lymphocytes	NA (<i>in vitro</i>)	0, 0.7, 7, 70, 700 μ M	96%	Positive at all doses (increase in tail length only)	Alvarez-Moya <i>et al.</i> , (2014)	Issues were identified with this study resulting in a low quality ranking. These include: 1) blood was washed with PBS and then held at 4° C for an indeterminate amount of time before exposure to glyphosate. (2) Cells were treated for 20 hours at room temperature. (3) The same amount of damage was reported across 2 orders of magnitude concentration.
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Human lymphocytes; $\pm$ S9 Alkaline and hOOG1 Comet assays performed	NA (<i>in vitro</i>)	0, 0.5, 2.91, 3.5, 92.8 and 580 μ g/mL	98%	Positive $\pm$ S9	Mladinic <i>et al.</i> (2009a)	<u>The alkaline comet assay</u> -S9: $\uparrow$ in mean tail length at 580 μg/mL and $\uparrow$ in tail intensity at $\geq$ 3.5 μg/mL). +S9: $\uparrow$ DNA tail length at $\geq$3.5 μg/mL. Tail intensity $\uparrow$ only at 580 μg/mL <u>hOOG1 comet assay:</u> -S9 no effect on tail length, $\uparrow$tail intensity only at 3.50 μg/mL +S9: $\uparrow$ tail length at 580 μg/mL, no effect on tail intensity compared to controls at any conc.

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.							
Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Single-cell gel electrophoresis (SCGE) assays- Comet assay with oxidative stress measures	Balb/C mice; evaluated blood and liver	Drinking water (14 days)	0, 40, and 400 mg/kg	96%	Positive Blood and liver at both doses	Manas <i>et al.</i> (2013)	Only minor effects seen on oxidative stress measurements (TBARs, SOD, CAT)
Sister Chromatid Exchange (SCE)	Bovine lymphocytes (3 donors)	NA (<i>in vitro</i>)	-S9: 0, 17, 85 and 170 µM; 72 h exposure	≥98%	Positive Significant (p>0.05) increase in SC/cell at all concentrations	Lioi (1998b)	1.8-, 2.1-, 1.6-fold increases, respectively
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (<i>in vitro</i>)	-S9: 0, 5, 8.5, 17 and 51 µM; 72 h exposure	≥98%	Positive Significant (p>0.05) increase in SCE/cell at ≥ 8.5 µM	Lioi (1998a)	1.9-, 2.8-, and 2.6-fold increase at 8.5, 17 and 51 µM, respectively
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (<i>in vitro</i>)	-S9: 0, 0.33, 1,3 and 6 mg/mL; 72 h exposure	99.9%	Positive	Bolognesi <i>et al.</i> (1997)	Very limited information was provided on the methods used in this paper. Authors report a dose –dependent increase in SCE frequency; however, no statistical analysis for dose response was reported. Data presented graphically with no error bars.
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (<i>in vitro</i>)	28, 56, 140, 280, 560 and 1120 µM; 24 h exposure ±S9	62%	Positive	Sivikova and Dianovsky (2006)	The increases in SCEs observed did not show a clear concentration related increase across a 40-fold increase in the concentrations tested

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Alkaline elution assay- DNA single strand breaks	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 8 and 24 h after injection	0, 300 mg/kg (3/dose)	99.9%	Positive (Increased elution rate) at 4 hours in liver and kidney At 24 h, elution rate returned to control levels	Bolognesi <i>et al.</i> (1997)	Return to control values may indicate DNA repair or reflect rapid elimination of compound
DNA Repair Test (Rec-A test)	<i>B. subtilis</i> H17 (rec+) and M45 (rec-)	NA (<i>in vitro</i>)	20-2000 µg/disk	98.4%	Negative	Shirasu (1978) [MRID 00078619]	
Unscheduled DNA synthesis (DNA repair)	F-344 rat primary hepatocytes	NA (<i>in vitro</i>)	0, 0.0125, 0.0625, 0.125, 0.6.5, 1.25, 12.5, 125 µg/mL	98%	Negative	Li and Long (1988)	
Cell Transformation Assay	BALB/3T cells	NA (<i>in vitro</i>)	0.313-5.0 mg/mL	90% Glyphosate trimesium salt	Negative	Majeska (1982b) [MRID 00126616]	

h- hour; CAT= catalase, G6PD= glucose 6-phosphate dehydrogenase, NA= not applicable, hOOG1= TBARs= thiobarbituric acid reactive substances, SOD= superoxide dismutase

5.7 Summary and Discussion

The genotoxic potential of glyphosate has been extensively investigated using a variety of test systems and genetic endpoints. This assessment focuses only on test systems that the agency considered relevant for assessing genotoxic risks in humans. The totality of the genetic toxicology information was evaluated using a weight of evidence approach to determine the genotoxic potential of glyphosate. This involves the integration of *in vitro* and *in vivo* results as well as an overall evaluation of the quality, consistency, reproducibility, magnitude of response, dose-response relationship and relevance of the findings. In the weight of evidence analysis, studies evaluating endpoints that measured gene mutations and chromosomal aberrations (i.e. permanent DNA damage) were given more weight than endpoints reflecting DNA events that may be transient or reversible such as primary DNA damage (e.g., comet assays). *In vivo* studies in mammals were given the greatest weight and more weight was given to doses and routes of administration that were considered relevant for evaluating genotoxic risk based on human exposure to glyphosate. Also, since the molecular mechanisms underlying the observation of SCEs are unclear and thus, the consequences of increased frequencies of SCEs are unclear, the data from this test were given low weight in the overall analysis. A summary of the various lines of evidence of considered in the weight of evidence evaluation for the genotoxic potential of the active ingredient glyphosate is presented below.

Evidence of primary DNA damage

Glyphosate technical is not considered to be electrophilic and did not induce DNA adducts in the liver or kidney at an i.p. dose of 270 mg/kg. However, evidence of DNA strand breaks was reported in a number mammalian cell studies using the comet assay. Additionally, transient increases in alkali labile sites in the liver and kidney of mice and an induction of 8-OHdG in DNA were seen in the livers of mice following i.p. injections with 300 mg/kg glyphosate. These effects were seen at high doses for the i.p. route in mice (LD₅₀ for mouse =130 mg/kg; NTP, 1992). However, due to technical limitations identified in a number of these studies (e.g. use of cancer cell lines that have not been well-characterized, atypical exposure protocols and no indication of blind to treatment), caution should be exercised in interpreting the results.

In vitro mutations

Glyphosate technical was negative in all 39 studies for mutagenicity in bacteria. In the four studies that tested for gene mutations in mammalian cells *in vitro*, no increase in mutations were observed.

In vitro chromosomal alterations

Mixed results were observed in studies evaluating *in vitro* chromosomal alterations with glyphosate treatment. Three SCE studies reported positive findings (Lioi, 1998a, b; Bolognesi *et al.*, 1997) bovine and human lymphocytes. As stated previously, low weight is given to SCE results in the overall analysis given the uncertainty regarding the consequence of increases in the frequencies of SCEs. The SCE responses were weak and not concentration dependent. Eight of the 10 studies measuring *in vitro* chromosomal aberrations were negative. The two positive

findings were reported by Lioi *et al.*, one study was conducted with bovine lymphocytes and the other with human lymphocytes. The authors reported positive findings in these studies at concentrations much lower than four other studies that reported negative results using the same cell types. Additionally, in both studies, Lioi *et al.* used an atypical exposure protocol of 72 hours which is very long for analyzing one round of mitosis. Furthermore, in both studies, nearly the same level effect for aberration frequency and percent of cells with aberrations were observed for the same concentrations of glyphosate and the two other chemicals tested in those experiments.

Four of the six studies evaluating micronuclei induction *in vitro* were positive and two showed equivocal results. Three of the positive responses required S9 activation, two conducted with human lymphocytes and one conducted with CHO cells. The remaining positive micronucleus study was conducted using a TR146 cells which is a tumor cell line derived from human buccal mucosa. The authors state that this cell line had not been previously used for genotoxicity testing. It is difficult to interpret any genotoxicity findings conducted in a tumor cell line that has not been well-characterized regarding its DNA damage response and repair capacity, and its degree of chromosomal instability.

Glyphosate was negative in all three L5178Y mouse lymphoma cell studies which may detect chromosomal damage in addition to mutations.

Mammalian *in vivo* chromosomal alterations

All three *in vivo* mammalian studies evaluating chromosomal aberrations with glyphosate technical were negative. Two studies were conducted in rats (i.p. and oral) and one was conducted in mice (oral). In addition, glyphosate was also negative in a rodent dominant lethal test. Glyphosate was negative in 15 of the 19 bone marrow micronucleus studies evaluated. In two of the positive studies, glyphosate technical was administered by i.p. injection. In these studies, the authors reported positive findings at doses of 200-300 mg/kg. Based on the available ADME data for glyphosate, assuming 30% oral absorption, an oral dose of ~700-1000 mg/kg would be needed to achieve a dose of 200-300 mg/kg in the blood. Seven other i.p. studies in mice reported no increase in micronuclei induction at doses up to 3000 mg/kg. The remaining positive finding was reported in an oral gavage study in mice where an approximately 2-fold increase in micronuclei were reported in females only at a dose of 5000 mg/kg, which is considerably higher than the current guideline recommended limit dose of 2000 mg/kg. The effect was not seen in the 7 other oral gavage studies in mice when glyphosate was tested at similar doses. In addition, glyphosate was negative for micronuclei induction following a 13-week dietary study with a dose up to approximately 3000 mg/kg/day. A negative finding was also reported in the only study that evaluated *in vivo* micronuclei induction in the rat using doses up to 2000 mg/kg.

In a meta-analytic review of micronuclei frequency across mammalian and non-mammalian species (primarily fish, amphibians, reptiles and plants), Ghisi *et al.* (2016), not surprisingly, reported that different responses were observed when comparing mammalian results to phylogenetically distant non-mammalian species for micronuclei induction. Their analyses included most, but not all, of the mammalian studies that the agency evaluated and determined to

be negative for micronuclei induction. The authors reported a statistically significant increase in micronuclei by the i.p. route across the studies in the data set they considered; however, when glyphosate was administered by the oral route (which is the most physiologically relevant route for human exposure to glyphosate), no significant difference was observed.

Conclusion for Glyphosate

The overall weight of evidence indicates that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route. When administered by i.p. injection, the micronucleus studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route, the effects occurred above the reported i.p. LD50 for mice and were not observed in other i.p. injection studies at similar or higher doses. While there is limited evidence genotoxic 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.

6.0 Data Integration & Weight-of-Evidence Analysis Across Multiple Lines of Evidence

6.1 Background

In 2010, OPP developed a draft “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment” which provides the foundation for evaluating multiple lines of scientific evidence (U.S. EPA, 2010). In 2016, a final version of the framework was published. OPP’s framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety MOA/human relevance framework, which highlights the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek et al, 2014).

One of the key components of the agency’s framework is the use of modified Bradford Hill Criteria (Hill, 1965) like those described in the 2005 Guidelines for Carcinogen Risk Assessment. These criteria are used to evaluate the experimental support considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight-of-evidence analysis.

6.2 Dose-Response and Temporal Concordance

Given the lack of consistent positive findings particularly at doses < 1000 mg/kg/day across the lines of evidence, lack of mechanistic understanding, and lack of biological activity in mammalian systems to the parent compound glyphosate, there are few data to assess key events in the biological pathway and any associated temporal or dose concordance. Temporal concordance can be assessed using the experimental animal studies and epidemiological studies that evaluated exposure prior to outcomes. Similarly, dose concordance can be assessed using findings of apical outcomes in experimental animal studies, as well as epidemiological studies that utilize exposure metrics that are stratified by the number of exposure days.

A prospective cohort study is designed to collect exposure information prior to the development of cancer. As such, exposure is known to occur before the outcome. In De Roos *et al.* (2005), a prospective cohort study, no association was observed between glyphosate exposure and all cancer outcomes evaluated in the AHS cohort. Although the median follow-up time following recruitment into the cohort was approximately 7 years in De Roos *et al.* (2005), an updated analysis of the AHS cohort has been recently published (Andreotti *et al.*, 2017), which included an extended follow-up period of 17.5 years and also did not report an association between glyphosate exposure and all cancer outcomes evaluated.

Two case-control studies evaluating the risk of NHL (Eriksson *et al.*, 2008 and McDuffie *et al.*, 2001) observed increased effect estimates in the highest exposure categories analyzed. Eriksson *et al.* (2008) found a greater effect estimate for subjects with >10 days (based on the median days of exposure among controls) and >10 years of exposure (for latency analysis) when compared to subjects with ≤10 days and 1-10 years of exposure, respectively; however, this analysis did not appear to adjust for co-exposures to other pesticides. By dividing the total number of exposed cases and controls using these exposure metrics, wider confidence intervals were observed due to smaller sample sizes, which reduces the reliability of the results to demonstrate a true

association. This may indicate that a longer follow-up time is needed to detect the risk for NHL; however, given the latency analysis of NHL was limited to Eriksson *et al.* (2008) and lack of NHL latency understanding in general, further studies are needed to determine the true latency of NHL. McDuffie *et al.* (2001), stratifying based on the average number of days per year of exposure, observed similar effect estimates in the lower exposure category (>0 and ≤ 2 days/year) while a greater effect estimate was observed in the highest exposure category (>2 days/year). The results from these two case-control studies conflict with the results observed in the cohort study (De Roos *et al.*, 2005; Andreotti *et al.*, 2017), where no dose-response was seen across three exposure categories (stratified by tertiles); however, the case-control studies did not adjust for co-exposure to other pesticides. It is also difficult to make conclusions regarding dose-response with only two exposure categories used for the analyses by Eriksson *et al.* (2008) and McDuffie *et al.* (2001). It should also be noted that these analyses combine all NHL subtypes, which may have etiological differences (Morton *et al.*, 2014). Although some studies did provide effect estimates for subtypes, as stated in Section 3.5.2, these were not considered in the current evaluation due to the limited sample sizes. At this time, there are no data available to evaluate dose-response for NHL subtypes.

With respect to animal carcinogenicity studies, key events in a MOA/AOP are evaluated to confirm that they precede tumor appearance. This temporal concordance evaluation cannot be conducted for glyphosate since a MOA/AOP has not been established. It was noted that no preneoplastic or related non-neoplastic lesions were reported in any of the animal carcinogenicity studies to support any observed tumors. Furthermore, genotoxicity assays did not support a direct mutagenic MOA. While there is limited evidence of genotoxicity in some *in vitro* endpoints, multiple *in vivo* studies do not support a genotoxic risk at relevant human exposure levels.

6.3 Strength, Consistency, and Specificity

A large database is available for evaluating the carcinogenicity potential of glyphosate. Across animal carcinogenicity and genotoxicity studies, results were consistent. For epidemiological studies, only one or two studies were available for almost all cancers investigated. The largest number of studies was available investigating NHL; however, there were conflicting results across studies.

In epidemiological studies, there was no evidence of an association between glyphosate exposure and solid tumors, leukemia, and HL. This conclusion is consistent with those recently conducted by IARC, EFSA, and JMPR. Furthermore, the available studies do not link glyphosate exposure to multiple myeloma.

At this time, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be supported based on the available data due to conflicting results. Chance and/or bias cannot be excluded as an explanation for observed associations. The magnitude of adjusted risk estimates for ever/never use were relatively small ranging from 1.0 (no association) to 1.85 in adjusted analyses, with the widest confidence intervals observed for the highest effect estimates indicating less reliability in these estimates. All of the ever/never estimates were not statistically significant with several effect estimates approximately equal to the null. There were

various limitations identified in Section 3.6 for these studies that could impact calculated effect estimates and explain the weak responses observed. Meta-risk ratios using these studies were also of small magnitude ranging from 1.3-1.5. As discussed in Section 3.6, meta-analyses should be interpreted with caution and are susceptible to the same limitations identified for individual studies.

Although none of the effect estimates were below 1 using the ever/never exposure metric, risk estimates were all below 1 (0.6-0.9) when using cumulative lifetime and intensity-weighted cumulative exposure metrics in the prospective cohort study (De Roos *et al.*, 2005; Andreotti *et al.*, 2017). As discussed in Section 6.2, two case-control studies that investigated an exposure-response relationship conflicted with the extensive analyses conducted for the AHS cohort. This may be due to differences in confounding control, differences associated with study design, limitations from small sample sizes, and/or, as some may suggest, a potentially short follow-up time in the cohort. It should also be noted that publication bias may play a role in this evaluation given there is a tendency to only publish positive results and potential concerns regarding glyphosate have only been raised in recent years.

A total of 14 (8 rat and 6 mouse) animal carcinogenicity studies with glyphosate, glyphosate acid, or glyphosate salts were analyzed for the current evaluation. None of the tumors evaluated were considered to be treatment-related based on weight-of-evidence evaluations. Although statistically significant trends were observed following adjustment for multiple comparisons in a limited number of studies, statistically significant pairwise comparisons were only observed in 2 studies indicating tumor incidences were generally similar to concurrent controls. Additionally, none of the tumor results were reproduced in other studies, including those testing the same animal strain with similar or higher dosing. Furthermore, the tumors lacked a monotonic dose-response and/or corroborating preneoplastic or related non-neoplastic lesions.

Over 80 genotoxicity studies with the active ingredient glyphosate were analyzed for the current evaluation. The overall weight-of-evidence indicates that there is no convincing evidence that glyphosate is genotoxic *in vivo* via the oral route. When administered via i.p. injection the studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route, the effects were not observed in other i.p. injection studies at similar or higher doses. Technical glyphosate was negative in all gene mutation studies. There was limited evidence of positive findings in studies evaluating primary DNA damage; however, as discussed in Section 5.6, the endpoints measured in these assays are less specific in regards to detecting permanent DNA changes (mutations) and can be attributed to other factors, such as cytotoxicity or cell culture conditions. Although some positive findings were reported for chromosomal alterations *in vitro*, these findings were limited to a few studies and are not supported by the *in vivo* studies that are the most relevant for human risk assessment.

Overall, there is remarkable consistency in the database for glyphosate across multiple lines of evidence. For NHL, observed associations in epidemiological studies were non-statistically significant and were of relatively small magnitude. Chance and/or bias cannot be excluded as an explanation for the observed associations. For all other cancer types, there were no associations found; however, only one or two studies were available for evaluation of most cancer types. Across species, strain, and laboratory, none of the tumors evaluated were considered to be

treatment-related based on weight-of-evidence evaluations. Statistically significant tumor results seen in individual studies were not reproduced in other studies, including those conducted using the same strain at similar or higher doses. The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic *in vivo*.

6.4 Biological Plausibility and Coherence

The Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) include the following guidance regarding the criteria of biological plausibility and coherence:

“evaluation of the biological plausibility of the associations observed in epidemiologic studies reflects consideration of both exposure-related factors and toxicological evidence relevant to identification of potential modes of action (MOAs). Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the biological markers evaluated in toxicologic and epidemiologic studies. [p.39].”

The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic *in vivo*. Immunodeficiency is another plausible MOA associated with tumorigenesis (i.e., altered immune surveillance). Glyphosate was negative in an immunotoxicity study in mice at doses up to 1448 mg/kg/day (MRID 48934207). Additionally, the toxicology database for glyphosate does not reveal any evidence of immunotoxicity. Overall, the available data regarding non-cancer endpoints also do not provide any support for a carcinogenic process for glyphosate, and have shown glyphosate has relatively low toxicity. Laboratory animals generally display non-specific effects (e.g., clinical signs, reduced body weight) following glyphosate exposure at relatively high-doses, and no preneoplastic or related non-neoplastic lesions were observed to corroborate any of the observed tumors in the carcinogenicity studies.

As discussed in Section 4.2, metabolism studies demonstrate low oral absorption and rapid excretion of glyphosate. The data are not sufficient to determine whether linear kinetics is occurring at high doses where tumors were observed. In the carcinogenicity test guideline (OCSPP 870.4200) and the 2005 Guidelines for Carcinogen Risk Assessment, inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A study evaluating the toxicokinetic profile of glyphosate using multiple doses is needed to further investigate the pharmacokinetic properties between low- and high-dose levels.

Although many of the studies included in this document focus on the potential for glyphosate to cause a cancer outcome, the agency is also aware of a limited number of studies in the open literature that have shown glyphosate and its metabolite, AMPA, can inhibit proliferation and promote apoptosis in cancer cells indicating the compounds have potential to be developed into therapeutic drugs for cancer treatment (Li *et al*, 2013; Parajuli *et al.*, 2015; Parajuli *et al.*, 2016). It is unknown if this is due to lack of additional studies that have investigated these compounds for cancer treatment or if this may be due to publication bias. The bias towards only publishing positive and/or novel results can hamper the ability to evaluate whether there are plausible biological mechanisms for observed outcomes and/or sufficient information to support a cause-and-effect interpretation of an association. Overall, this further supports the need for

mechanistic data to elucidate the true mammalian MOA/AOP for glyphosate. There is a distinct lack of mechanistic understanding for the toxicity of glyphosate in mammals and the plant MOA is not relevant for mammalian systems.

The agency does not consider any of the tumors observed in the animal carcinogenicity studies to be treatment-related; however, some believe that the increased tumor incidences in various studies at the highest doses tested are treatment-related. In almost all of these studies, the highest dose tested was approximately equal to or greater than the limit dose (1000 mg/kg/day). It is very unlikely for people to be exposed to such large doses of glyphosate via the oral route. Glyphosate is registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops, as well as desiccant applications to several commodities. The highest dietary exposure value for any population subgroup in an unrefined chronic dietary analysis would be 0.23 mg/kg/day for children (1-2 years old). Since glyphosate also has residential uses, including application to turf, there is also the potential for children at this age to be exposed via incidental oral exposures (e.g., hand to mouth, object to mouth and soil ingestion) from playing on treated lawns. The highest exposure for the incidental oral and dermal exposures would be 0.16 mg/kg/day (from hand-to-mouth behaviors for children) and 0.08 mg/kg/day, respectively. Combining exposures from the dietary and residential exposures for children would, therefore, result in an aggregate exposure of 0.47 mg/kg/day. These calculations use a number of assumptions that have been extensively peer-reviewed²⁷ and yet the potential oral exposure of glyphosate for the most highly exposed residential population subgroup is more than 2,000 times lower than the highest doses tested in the animal carcinogenicity studies (see Appendix E for more details regarding these calculations). The maximum potential exposure calculated for occupational handlers would be 7 mg/kg/day, which is still significantly lower than the highest doses tested in the animal carcinogenicity studies. As a result, even though increased tumor incidences were observed in some of the animal carcinogenicity studies, the possibility of being exposed to these excessive dietary doses over time is considered implausible based on the currently registered use pattern and not relevant to human health risk assessment.

6.5 Uncertainty

When evaluating a database, it is also important to assess the uncertainties associated with the available data. When uncertainty is high there is less confidence in the exposure and effect estimates and, therefore, informs the reliability of results. Understanding the sources of uncertainty within a database can help characterize observed results and aid in developing new research with reduced uncertainty.

In some instances, the agency did not have access to all of the data underlying the studies analyzed for the current evaluation. This includes all of the epidemiological studies, 17 genotoxicity studies, and 1 animal carcinogenicity study. For these studies, the agency had to rely upon information the study authors reported. Without the raw data, statistical analyses could not be replicated or recalculated. On the other hand, studies that include full reports with detailed methodology, analytically measured doses, and individual animal data may provide a

²⁷ Using the 2012 Standard Operating Procedures for Residential Exposure Assessment. Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

higher level of confidence. It also allows the agency to perform its own evaluation of the data using current practices and policies.

Several uncertainties have already been identified throughout this document. There are numerous metabolism studies available for glyphosate; however, the data are not sufficient to determine whether linear kinetics is occurring at high doses where tumors were observed in animal carcinogenicity studies. In the carcinogenicity test guideline (OCSPP 870.4200) and the 2005 Guidelines for Carcinogen Risk Assessment, inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A study evaluating the toxicokinetic profile of glyphosate using multiple doses is needed to further investigate the pharmacokinetic properties between low- and high-dose levels.

With respect to the epidemiological data, the database is limited for each investigated cancer with only one or two studies available. Although numerous studies were used in the evaluation of NHL, the results were constrained by the limitations of the individual studies, such as small sample size, missing data, and control selection issues. The quality of the exposure assessment is a major concern since the validity of the overall study results depend in large part on the ability of the study to correctly quantify and classify a subject's exposure. There was no direct information on pesticide exposure or absorbed dose because the exposures were self-reported. All of the studies conducted exposure assessments through questionnaires and interviews that are susceptible to recall bias, which can result in exposure misclassification. The cohort study (De Roos *et al.*, 2005), which was given a high ranking, did not find an association between glyphosate exposure and NHL; however, it has been noted that the median follow-up time for this study was ~7 years. Recently, an updated analysis was published (Andreotti *et al.*, 2017) with an extended follow-up period of 17.5 years that addresses concerns regarding follow-up time. This study reported no association between glyphosate exposure and all lymphohematopoietic cancers, NHL, or any of its subtypes across exposure metrics. No association was observed in unlagged or lagged analyses, after adjustment for pesticides linked to NHL in previous AHS analyses, and after exclusion of multiple myeloma from the NHL grouping. Furthermore, with the increased use of glyphosate following the introduction of glyphosate-tolerant crops in 1996, there is a need for more recent studies since a large number of studies were conducted prior to 1996. As described in Section 1.1, the use pattern changed following the introduction of transgenic crops, which may impact overall effect estimates.

Another consideration is that farmers and other applicators apply formulations, not the active ingredient alone. It is possible that different formulations were used across and/or within the different epidemiological studies. Formulations are end-use products that are sold as a mixture of registered pesticidal active ingredients, such as glyphosate, and additional substances that increase the effectiveness of a pesticidal product, which are often referred to as “inert ingredients.” For example, inert ingredients may act as a solvent to allow a pesticide active ingredient to penetrate a plant's outer surface, may facilitate and accentuate the dispersion of the product, or may extend the pesticide product's shelf-life²⁸. Inert ingredients and the proportion of these inert ingredients vary across formulations. It has been hypothesized that glyphosate formulations may be more toxic than glyphosate alone. Glyphosate has been studied in a multitude of studies and there are studies that have been conducted on numerous formulations

²⁸ <https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance>

that contain glyphosate; however, there are relatively few research projects that have attempted to systematically compare glyphosate and the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations. This is one aspect of the uncertainty in the database that the agency has been working to address by developing a strategic research plan in collaboration with NTP (see Section 7.0).

It is recognized that these uncertainties exist for the current database; however, the available data are adequate for evaluating the carcinogenic potential of glyphosate and determine the cancer classification using the 2005 Guidelines for Carcinogen Risk Assessment. As discussed in Section 6.3, there are a large number of studies available and the database is remarkably consistent across these studies.

6.6 Evaluation of Cancer Classification per the 2005 EPA Guidelines for Carcinogen Risk Assessment

6.6.1 Introduction

In the 2005 Guidelines for Carcinogen Risk Assessment, five classification descriptors are provided:

- 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

Descriptors are assigned using all available data from the multiple lines of evidence. The following text has been excerpted/summarized from the guidelines regarding these descriptors:

Choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence. The weight-of-evidence, including the selected descriptor, is presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available. The descriptors and narratives are intended to permit sufficient flexibility to accommodate new scientific understanding and new testing methods. The descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full weight-of-evidence narrative. Rather than focusing simply on the descriptor, the entire range of information included in the weight-of-evidence narrative should be considered.

The weight-of-evidence presented in Sections 6.2-6.5 and based on the available epidemiological, animal carcinogenicity, and genotoxicity data for glyphosate was considered for each classification descriptor. For each descriptor, the guidelines provide examples and/or conditions for when the descriptor may be appropriate and the weight-of-evidence for glyphosate is assessed to determine which descriptor is supported by the available data. As stated in the 2005 EPA Guidelines for Carcinogen Risk Assessment, “the entire range of information included

in the weight-of-evidence should be considered”. Based on all of the available data, the weight-of-evidence clearly do not support the descriptors “carcinogenic to humans” and “likely to be carcinogenic to humans” at this time. According to the 2005 Cancer Guidelines, “carcinogenic to humans” is appropriate “when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.” Similarly, “likely to be carcinogenic to humans” descriptor is appropriate “when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor.”

In epidemiological studies, there was no evidence of an association between glyphosate exposure and solid tumors, leukemia, or HL. Furthermore, the available studies do not link glyphosate exposure to multiple myeloma. A conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data due to conflicting results and various limitations identified in studies investigating NHL. In 6 of the 14 animal carcinogenicity studies, no tumors were identified for evaluation. In the remaining 8 studies, the agency has concluded that none of the tumors evaluated in individual rat and mouse carcinogenicity studies are treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Tumors seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses. The tumor incidence increases in these studies were seen at or exceeding 1,000 mg/kg/day, except the testicular tumors in a single rat study, and these high doses would also not be considered relevant for human health risk assessment. The mammalian MOA/AOP is unknown for glyphosate and precursor events are unknown; however, the genotoxicity data were highly reproducible and consistent with a clear demonstration that glyphosate does not have a mutagenic MOA.

The descriptor “inadequate information to assess carcinogenic potential” is used when available data are judged inadequate for applying one of the other descriptors. Given the extensive size of the glyphosate database, which includes a multitude of well-designed and well-conducted studies, this classification descriptor is not supported. The epidemiological data at this time are limited and study results appear to be inconsistent for some cancer types. However, it is important to note that epidemiological studies are not available for most pesticides. Similarly, for most pesticides, generally, only two animal bioassays are available. EPA routinely evaluates human cancer potential using the small, more typical datasets. As such, for glyphosate, given the significant amount of information across multiple lines of evidence, the agency believes the database is sufficient to designate a cancer classification descriptor for glyphosate and that “inadequate information to assess carcinogenic potential” is not appropriate.

The remaining two cancer classification descriptors (“*Suggestive Evidence of Carcinogenic Potential*” and “*Not Likely to Be Carcinogenic to Humans*”) from the 2005 EPA Guidelines for Carcinogen Risk Assessment are described in detail below. Subsequently, these descriptors are discussed in the context of whether the available evidence do or do not support them.

“Suggestive Evidence of Carcinogenic Potential”

This descriptor is appropriate when a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. It covers a spectrum of

evidence associated with varying levels of concern for carcinogenicity. Depending on the extent of the database, additional studies may or may not provide further insights.

Some examples of when this descriptor may be appropriate include the following:

- If a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that 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 a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence;
- If there is a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed (when there is a high background rate of a specific tumor in animals of a particular sex and strain, then there may be biological factors operating independently of the agent being assessed that could be responsible for the development of the tumors). In this case, the reasons for determining that the tumors are not due to the agent are explained; or
- If there is a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.

“Not Likely to Be Carcinogenic to Humans”

This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each MOA in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic.

This descriptor would be appropriate if any of the following was observed:

- Animal evidence demonstrates 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, or
- Convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans, or
- Convincing evidence that carcinogenic effects are not likely by a particular exposure route, or
- Convincing evidence that carcinogenic effects are not likely below a defined dose range.

6.6.2 Discussion of Evidence to Support Cancer Classification Descriptors

As stated above, the available data and weight-of-evidence clearly do not support the descriptors “carcinogenic to humans”, “likely to be carcinogenic to humans”, or “inadequate information to assess carcinogenic potential”. The following discusses the remaining cancer classification descriptors and how the evidence does or does not support the descriptors.

It could be argued that the “suggestive evidence of carcinogenic potential” descriptor would be appropriate. The evidence to support this includes:

- Non-statistically significant effect estimates greater than the null were reported for NHL across studies and meta-analyses based on ever/never use ranged from 1.3-1.5.
- There was limited evidence of a possible exposure-response relationship between glyphosate exposure and NHL in case-control studies.
- In several animal carcinogenicity studies, a statistically significant trend was observed. In two studies, tumor incidences at the highest doses tested were statistically significant as compared to concurrent controls.
- Positive responses were observed in a limited number of genotoxicity assays evaluating chromosomal and primary DNA damage.

However, according to the 2005 EPA Guidelines for Carcinogen Risk Assessment, in order for the above evidence to support the “suggestive evidence of carcinogenic potential” descriptor, “the study generally would not be contradicted by other studies of equal quality in the same population group or experimental system”. Furthermore, the guidelines state that “rather than focusing simply on the descriptor, the entire range of information included in the weight-of-evidence narrative should be considered”. For the epidemiological studies evaluating NHL, several studies reported effect estimates approximately equal to the null. The widest confidence intervals were observed for the highest effect estimates indicating these effect estimates are less reliable. All of the effect ever/never estimates were non-statistically significant. There were conflicting results in exposure-response assessments investigating glyphosate exposure and the risk of NHL. Although two case control studies (McDuffie *et al.*, 2001; Eriksson *et al.*, 2008) reported elevated effect estimates when analyzing for exposure-response relationships across two exposure categories, extensive analyses in a study of equal or higher quality (De Roos *et al.*, 2005) for cumulative lifetime exposure and intensity-weighted cumulative exposure contradicted these results reporting effect estimates less than null (ranging from 0.6-0.9) when analyzing across tertiles and these analyses were further supported by the recent evaluation of the AHS cohort by Andreotti *et al.* (2017). Furthermore, the two case control studies did not account for co-exposure to other pesticides, which would be expected to cause inflated effect estimates. Various limitations that could impact the calculated effect estimate were identified for these studies and discussed in Section 3.6. The effect estimates greater than the null were not strengthened by other lines of evidence, as described in Sections 6.2-6.5.

In 6 (4 rat and 2 mouse) of the 14 animal carcinogenicity studies conducted with glyphosate, no tumors were identified for evaluation. In the remaining 8 studies, although statistically significant trends following adjustment for multiple comparisons were observed in 6 of these studies for different individual tumor types, almost all of these lacked pairwise significance

following adjustment for multiple comparisons. Pairwise significance was only observed at the highest dose tested for testicular tumors (Lankas, 1981) and hemangiomas (Sugimoto, 1997). For testicular tumors, a closer examination of the incidence data across doses did not demonstrate a monotonic dose response and the tumor findings were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. For hemangiomas, the statistical significance was seen at a dose more than 4X the limit dose, which would not be considered relevant for human health risk assessment. Furthermore, the tumor findings were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. In all of the animal carcinogenicity studies, there was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions to support a treatment-related effect, including the testicular tumors. In a limited number of cases, the agency also considered historical control data to inform the relevance of tumor findings and these data generally indicated that incidence rates in the concurrent controls were unusually low and/or observed tumor incidences were within historical control ranges.

Although positive responses were observed in a limited number of genotoxicity assays evaluating chromosomal and primary DNA damage, the overall weight-of-evidence indicates that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route. When administered via i.p. injection the studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route of administration, the results were contradicted by numerous other studies at similar or higher doses using the same assays and route of administration. Technical glyphosate was negative in all gene mutation studies. There was limited evidence of positive findings in studies evaluating primary DNA damage; however, the endpoints measured in these assays are less specific in regards to detecting permanent DNA changes (mutations) and can be attributed to other factors, such as cytotoxicity or cell culture conditions. Although some positive findings were reported for chromosomal alterations *in vitro*, these findings were limited to a few studies and are not supported by the *in vivo* studies that are the most relevant for human risk assessment.

In summary, considering the entire range of information for the weight-of-evidence, the evidence outlined above to potentially support the “suggestive evidence of carcinogenic potential” descriptor are contradicted by other studies of equal or higher quality and, therefore, the data do not support this cancer classification descriptor.

For the “not likely to be carcinogenic to humans” descriptor, one of the considerations is whether there is “convincing evidence that carcinogenic effects are not likely below a defined dose range”. In the case of glyphosate, the agency did not consider any of the tumors observed in the animal carcinogenicity studies to be treatment-related; however, some believe that the increased tumor incidences in various studies at the highest doses tested are treatment-related. In all of these studies, the highest dose tested was approximately equal to or greater than the limit dose (1000 mg/kg/day), except for the testicular tumors observed in a single study that were not considered treatment-related and were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. In genotoxicity studies, assays with oral administration were negative except for one instance where an extremely high dose (5,000 mg/kg/day) was administered.

The 2005 EPA Guidelines for Carcinogen Risk Assessment also state that “weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed”. Increased tumor incidence was typically observed at doses of 1,000 mg/kg/day or greater; however, none of these were considered treatment-related by the agency based on the weight-of-evidence evaluations. Additionally, the only *in vivo* positive assays seen in the genotoxicity studies were administered via i.p. injection at doses of 200 mg/kg/day and 300 mg/kg/day or orally at 5,000 mg/kg/day. These high doses are not considered relevant to human health risk assessment based on the currently registered use pattern for glyphosate. Maximum potential glyphosate exposure in residential and occupational settings have been estimated at 0.47 mg/kg/day and 7 mg/kg/day, respectively, which are well-below the doses necessary to elicit the effects seen in these animal carcinogenicity and genotoxicity studies. Additionally, non-linear kinetics may also be occurring at the high doses. The carcinogenicity test guidelines (OCSPP 870.4200 and OCSPP 870.4300) and the 2005 Guidelines for Carcinogen Risk Assessment state that inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A well-conducted pharmacokinetic study evaluating the toxicokinetic profile of glyphosate is needed to further investigate the toxicokinetic properties between high and low dose levels to ensure that inappropriate toxicokinetics is avoided.

Overall, there is not strong support for the “suggestive evidence of carcinogenic potential” cancer classification descriptor based on the weight-of-evidence, which includes the fact that even small, non-statistically significant changes observed in animal carcinogenicity and epidemiological studies were contradicted by studies of equal or higher quality. The strongest support is for “not likely to be carcinogenic to humans”.

6.7 Proposed Conclusions Regarding the Carcinogenic Potential of Glyphosate

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. Following the introduction of glyphosate-resistant crops in 1996, glyphosate use increased dramatically; however, glyphosate use has stabilized in recent years due to the increasing number of glyphosate-resistant weed species.

Since its registration in 1974, numerous human and environmental health analyses have been completed for glyphosate, which consider all anticipated exposure pathways. Glyphosate is currently undergoing Registration Review. As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health using current practices and policies. The human carcinogenic potential of glyphosate has been evaluated by the agency several times. As part of the current evaluation for Registration Review, the agency has performed a comprehensive analysis of available data from submitted guideline studies and the open literature. This includes epidemiological, animal carcinogenicity, and genotoxicity studies.

An extensive database exists for evaluating the carcinogenic potential of glyphosate, including 63 epidemiological studies, 14 animal carcinogenicity studies, and nearly 90 genotoxicity studies for the active ingredient glyphosate. These studies were evaluated for quality and results were analyzed across studies within each line of evidence. The modified Bradford Hill criteria were then used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance and biological plausibility. The available data at this time do not support a carcinogenic process for glyphosate. Overall, animal carcinogenicity and genotoxicity studies were remarkably consistent and did not demonstrate a clear association between glyphosate exposure and outcomes of interest related to carcinogenic potential. In epidemiological studies, there was no evidence of an association between glyphosate exposure and numerous cancer outcomes; however, due to conflicting results and various limitations identified in studies investigating NHL, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. Increases in tumor incidence were not considered treatment-related in any of the animal carcinogenicity studies. In 6 of these studies, no tumors were identified for evaluation. In the remaining studies, the tumors were not considered treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Additionally, tumor findings seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses. Furthermore, data from epidemiological and animal carcinogenicity studies do not reliably demonstrate expected dose-response relationships. In genotoxicity studies, there was no convincing evidence that glyphosate is genotoxic *in vivo* via the oral route.

For cancer descriptors, the available data and weight-of-evidence clearly do not support the descriptors “carcinogenic to humans”, “likely to be carcinogenic to humans”, or “inadequate information to assess carcinogenic potential”. For the “suggestive evidence of carcinogenic potential” descriptor, considerations could be looked at in isolation; however, following a thorough integrative weight-of-evidence evaluation of the available data, the database would not support this cancer descriptor. The strongest support is for “not likely to be carcinogenic to humans”.

This analysis integrating multiple lines of evidence highlights the need for mechanistic studies to elucidate the MOA/AOP of glyphosate, as well as additional epidemiology studies and updates from the AHS cohort study to further investigate the carcinogenic potential of glyphosate in humans. This evaluation focused on studies on the active ingredient glyphosate; however, additional research could also be performed to determine whether formulation components, such as surfactants, influence the toxicity of glyphosate formulations. The agency has been working on plans to initiate research given these identified data gaps and these plans are described in Section 7.0.

7.0 Collaborative Research Plan for Glyphosate and Glyphosate Formulations

As previously mentioned, some have believed that glyphosate formulations may be more toxic than glyphosate alone. Glyphosate has been studied in a multitude of studies and there are studies that have been conducted on numerous formulations that contain glyphosate; however, there are relatively few research projects that have attempted to directly compare glyphosate and the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations.

The agency has been collaborating with the NTP Division of the National Institute of Environmental Health Sciences to develop a research plan intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity. Four objectives were identified that laid out how research by NTP might contribute to these research questions: 1) compare the toxicity of glyphosate vs. formulations, as well as compare formulations vs. formulations, 2) provide publicly available toxicology data on cancer-related endpoints, 3) provide publicly available toxicology data on non-cancer endpoints, and 4) investigate the mechanisms of how glyphosate and formulations cause toxic effects.

As part of the first objective, NTP will investigate the differential biological activity of glyphosate, glyphosate formulations, and the individual components of formulations. The NTP Laboratory Branch generated preliminary data by exposing human hepatoma cells (HepG2) to five different glyphosate products bought off the shelf. The endpoint in the assay was cell viability, measured by ATP levels. The data, presented in Figure 7.1, demonstrate at-a-glance that formulations are not equally toxic and that the toxicity is not being driven by the amount of glyphosate in the formulations, at least for the endpoint of cell viability. This observation highlights how informative the data generated from this research can be to the overall research questions.

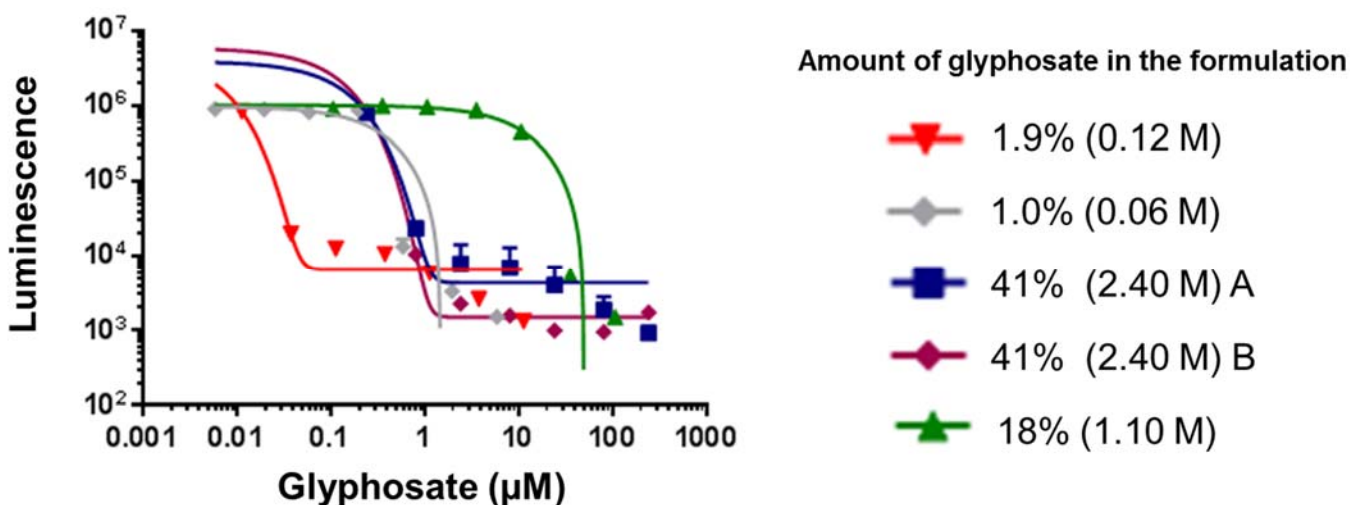


Figure 7.1. Results of HepG2 exposures following 24 hour incubation using different glyphosate formulations. Note: some of the formulations included other active ingredients besides glyphosate.

For the second objective, NTP will contribute to the publicly available knowledge-base describing the biological effects of glyphosate and formulations by conducting guideline studies addressing genotoxicity and studies that evaluate the oxidative stress potential. In order to organize publicly available data on glyphosate and formulations, IARC used 10 key characteristics of carcinogens as a way to help inform their conclusion (Smith *et al.*, 2016). Their review concluded that data were only available for two of these characteristics (genotoxicity and oxidative stress) and little to no information on the remaining characteristics was available. However, when members of a NTP workgroup looked at the available data included in the IARC review, the group did not agree with IARC that the data provided strong or clear evidence for either genotoxicity or induction of oxidative stress given protocol deficiencies that could produce questionable results.

Currently, the publicly available information regarding non-cancer endpoints for glyphosate and glyphosate formulations is limited. To begin to address the third objective, NTP will conduct a screening level analysis of the literature using text mining software, for studies regarding non-cancer endpoints resulting from glyphosate exposure. The resulting scoping report will describe the evidence base for health outcomes investigated in connection to glyphosate, as well as help identify data gaps.

As discussed in Section 6.0, there is a need for mechanistic studies to elucidate the MOA/AOP of glyphosate. Although there are data suggesting glyphosate may be genotoxic or cause oxidative stress, there is little mechanistic information to support these observations. For the last objective, NTP will use *in vitro* screening assays to gain mechanistic information on the effects of glyphosate and different formulations for a variety of endpoints and allow for direct comparisons among them. The screening approach will also allow for the identification of test substances that would be good candidates for further *in vivo* testing. Since *in vivo* findings in genetic toxicology testing are generally considered as having a greater relevance to humans than *in vitro* findings, it is valuable to confirm the results seen at the cellular level at the whole animal level.

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Appendix A. Journal articles obtained from open literature search

Abstract Only	Cebollero, L. R., et al. (2011). "Glyphosate based herbicides toxicity, a new approach." <i>Toxicology Letters</i> 205, Supplement: S233.
Abstract Only	Monroy, C. M., et al. (2004). "In vitro evaluation of glyphosate-induced DNA damage in fibrosarcoma cells HT1080 and Chinese hamster ovary (CHO) cells." <i>Environ Mol Mutagen</i> 44(3): 216-216.
Abstract Only	Ramos-Morales, P., et al. (2008). "Combined use of multiple biomarkers to evaluate the genotoxic activity of the herbicide Glyphosate." <i>Environ Mol Mutagen</i> 49(7): 577-577.
Abstract Only/Full article already identified	Sorahan, T. (2015). "Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data." <i>Int J Environ Res Public Health</i> 12(2): 1548-1559.
Article not in English	Kwiatkowska, M., et al. (2013). "GLYPHOSATE AND ITS FORMULATIONS - TOXICITY, OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE." <i>Med Pr</i> 64(5): 717-729.
Article not in English	Lawson, R. and E. Estrade-Chapellaz (1999). "Intoxication volontaire par le glufosinate (Basta®)." <i>Annales Françaises d'Anesthésie et de Réanimation</i> 18(9): 1025-1026.
Article not in English	Mañas, F., et al. (2009). "Aberraciones cromosómicas en trabajadores rurales de la Provincia de Córdoba expuestos a plaguicidas." <i>BAG. Journal of basic and applied genetics</i> 20(1): 0-0.
Article not in English	Martinez, A., et al. (2007). "[Cytotoxicity of the herbicide glyphosate in human peripheral blood mononuclear cells]." <i>Biomedica</i> 27(4): 594-604.
Article not in English	Monroy, C. M., et al. (2005). "[Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate]." <i>Biomedica</i> 25(3): 335-345.
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Not Relevant to current fit for purpose review	Owczarek, M., et al. (1999). "Evaluation of toxic and genotoxic activity of some pesticides in a soil-plant system." <i>Human and Environmental Exposure to Xenobiotics</i> : 755-762.
Not Relevant to current fit for purpose review	Perez-Iglesias, J. M., et al. (2016). "Effects of glyphosate on hepatic tissue evaluating melanomacrophages and erythrocytes responses in neotropical anuran <i>Leptodactylus latinasus</i> ." <i>Environ Sci Pollut Res Int</i> .
Not Relevant to current fit for purpose review	Poletta, G. L., et al. (2009). "Genotoxicity of the herbicide formulation Roundup (glyphosate) in broad-snouted caiman (<i>Caiman latirostris</i>) evidenced by the Comet assay and the Micronucleus test." <i>Mutat Res</i> 672(2): 95-102.
Not Relevant to current fit for purpose review	Siddiqui, S., et al. (2012). "Glyphosate, alachor and maleic hydrazide have genotoxic effect on <i>Trigonella foenum-graecum</i> L." <i>Bull Environ Contam Toxicol</i> 88(5): 659-665.
Not Relevant to current fit for purpose review	Song, H.-Y., et al. (2012). "Cellular Toxicity of Surfactants Used as Herbicide Additives." <i>J Korean Med Sci</i> 27(1): 3-9.
Not Relevant to current fit for purpose review	Unver, T., et al. (2010). "Genome-wide profiling and analysis of <i>Festuca arundinacea</i> miRNAs and transcriptomes in response to foliar glyphosate application." <i>Mol Genet Genomics</i> 283(4): 397-413.
Relevant- Cancer Epi	Acquavella, J. F., et al. (2006). "Exposure misclassification in studies of agricultural pesticides - Insights from biomonitoring." <i>Epidemiology</i> 17(1): 69-74.
Relevant- Cancer Epi	Acquavella, J. F., et al. (2005). "Implications for epidemiologic research on variation by pesticide in studies of farmers and their families." <i>Scandinavian Journal of Work Environment & Health</i> 31: 105-109.
Relevant- Cancer Epi	Baker, B. A., et al. (2005). "Farm Family Exposure Study: methods and recruitment practices for a biomonitoring study of pesticide exposure." <i>Journal of Exposure Analysis and Environmental Epidemiology</i> 15(6): 491-499.
Relevant- Cancer Epi	Chang, E. T. and E. Delzell (2016). "Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers." <i>J Environ Sci Health B</i> 51(6): 402-434.
Relevant- Cancer Epi	De Roos, A. J., et al. (2005). "Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study." <i>Environ Health Perspect</i> 113(1): 49-54.

Relevant- Cancer Epi	Firth, H. M., et al. (2007). "Chemical exposure among NZ farmers." <i>International Journal of Environmental Health Research</i> 17(1): 33-43.
Relevant- Cancer Epi	Lash, T. L. (2007). "Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty." <i>J Occup Med Toxicol</i> 2: 15.
Relevant- Cancer Epi	Mink, P. J., et al. (2012). "Epidemiologic studies of glyphosate and cancer: a review." <i>Regul Toxicol Pharmacol</i> 63(3): 440-452.
Relevant- Cancer Epi	Sorahan, T. (2012). "Multiple myeloma and glyphosate use: A re-analysis of US Agricultural Health Study data." <i>Toxicology Letters</i> 211, Supplement: S169.
Relevant- Carcinogenicity	Greim, H., et al. (2015). "Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies." <i>Crit Rev Toxicol</i> 45(3): 185-208.
Relevant- Carcinogenicity	Williams, G. M., et al. (2000). "Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient, Glyphosate, for Humans." <i>Regulatory Toxicology and Pharmacology</i> 31(2): 117-165.
Relevant- Genotoxicity	Alvarez-Moya et al. (2014) "Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms". <i>Genetics and Molecular Biology</i> , 37, 1, 105-110
Relevant- Genotoxicity	Chan, P. and J. Mahler (1992). "NTP technical report on the toxicity studies of Glyphosate (CAS No. 1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice." <i>Toxic Rep Ser</i> 16: 1-d3.
Relevant- Genotoxicity	Bakry, F. A., et al. (2015). "Glyphosate herbicide induces genotoxic effect and physiological disturbances in <i>Bulinus truncatus</i> snails." <i>Pestic Biochem Physiol</i> 123: 24-30.
Relevant- Genotoxicity	Bolognesi, C., et al. (1997). "Genotoxic activity of glyphosate and its technical formulation roundup." <i>J Agric Food Chem</i> 45(5): 1957-1962.
Relevant- Genotoxicity	Bolognesi, C., et al. (2009). "Biomonitoring of genotoxic risk in agricultural workers from five colombian regions: association to occupational exposure to glyphosate." <i>J Toxicol Environ Health A</i> 72(15-16): 986-997.
Relevant- Genotoxicity	Da Silva, F. R., et al. (2014). "Genotoxic assessment in tobacco farmers at different crop times." <i>Science of the Total Environment</i> 490: 334-341.
Relevant- Genotoxicity	Dimitrov, B. D., et al. (2006). "Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems." <i>Mutagenesis</i> 21(6): 375-382.
Relevant- Genotoxicity	El-Shenawy, N. S. (2009). "Oxidative stress responses of rats exposed to Roundup and its active ingredient glyphosate." <i>Environ Toxicol Pharmacol</i> 28(3): 379-385.
Relevant- Genotoxicity	Fortes, C., et al. (2016). "Occupational Exposure to Pesticides With Occupational Sun Exposure Increases the Risk for Cutaneous Melanoma." <i>J Occup Environ Med</i> 58(4): 370-375.
Relevant- Genotoxicity	Ghisi Nde, C., et al. (2016). "Does exposure to glyphosate lead to an increase in the micronuclei frequency? A systematic and meta-analytic review." <i>Chemosphere</i> 145: 42-54.
Relevant- Genotoxicity	Heydens, W. F., et al. (2008). "Genotoxic potential of glyphosate formulations: mode-of-action investigations." <i>J Agric Food Chem</i> 56(4): 1517-1523.
Relevant- Genotoxicity	Kale, P. G., et al. (1995). "MUTAGENICITY TESTING OF 9 HERBICIDES AND PESTICIDES CURRENTLY USED IN AGRICULTURE." <i>Environ Mol Mutagen</i> 25(2): 148-153.
Relevant- Genotoxicity	Kier, L. D. (2015). "Review of genotoxicity biomonitoring studies of glyphosate-based formulations." <i>Crit Rev Toxicol</i> 45(3): 209-218.
Relevant- Genotoxicity	Koller, V. J., et al. (2012). "Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells." <i>Arch Toxicol</i> 86(5): 805-813.
Relevant- Genotoxicity	Li, A. P. and T. J. Long (1988). "An evaluation of the genotoxic potential of glyphosate." <i>Fundam Appl Toxicol</i> 10(3): 537-546.
Relevant- Genotoxicity	Lioi, M. B., et al. (1998). "Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro." <i>Mutat Res</i> 403(1-2): 13-20.
Relevant- Genotoxicity	Manas, F., et al. (2009). "Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests." <i>Ecotoxicol Environ Saf</i> 72(3): 834-837.
Relevant- Genotoxicity	Manas, F., et al. (2009). "Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests." <i>Environmental Toxicology and Pharmacology</i> 28(1): 37-41.
Relevant- Genotoxicity	Mandel, J. S., et al. (2005). "Biomonitoring for farm families in the farm family exposure study." <i>Scandinavian Journal of Work Environment & Health</i> 31: 98-104.
Relevant- Genotoxicity	Mladinic, M., et al. (2009). "Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro." <i>Environ Mol Mutagen</i> 50(9): 800-807.

Relevant- Genotoxicity	Mladinic, M. and D. Zeljezic (2008). "Assessment of oxidative DNA damage by glyphosate applying hOGG1 modified comet and micronucleus assay." <i>Toxicology Letters</i> 180: S170-S171.
Relevant- Genotoxicity	Paz-y-Mino, C., et al. (2011). "Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border." <i>Rev Environ Health</i> 26(1): 45-51.
Relevant- Genotoxicity	Paz-y-Mino, C., et al. (2007). "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate." <i>Genetics and Molecular Biology</i> 30(2): 456-460.
Relevant- Genotoxicity	Peluso, M., et al. (1998). "32P-postlabeling detection of DNA adducts in mice treated with the herbicide Roundup." <i>Environ Mol Mutagen</i> 31(1): 55-59.
Relevant- Genotoxicity	Piesova, E. (2005). "The effect of glyphosate on the frequency of micronuclei in bovine lymphocytes in vitro." <i>Acta Veterinaria-Beograd</i> 55(2-3): 101-109.
Relevant- Genotoxicity	Prasad, S., et al. (2009). "Clastogenic effects of glyphosate in bone marrow cells of swiss albino mice." <i>J Toxicol</i> 2009: 308985.
Relevant- Genotoxicity	Rank, J., et al. (1993). "Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, Salmonella mutagenicity test, and Allium anaphase-telophase test." <i>Mutat Res</i> 300(1): 29-36.
Relevant- Genotoxicity	Roustan, A., et al. (2014). "Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation." <i>Chemosphere</i> 108: 93-100.
Relevant- Genotoxicity	Silva Kahl, V. F., et al. (2016). "Telomere measurement in individuals occupationally exposed to pesticide mixtures in tobacco fields." <i>Environ Mol Mutagen</i> 57(1): 74-84.
Relevant- Genotoxicity	Sivikova, K. and J. Dianovsky (2006). "Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes." <i>Int J Hyg Environ Health</i> 209(1): 15-20.
Relevant- Genotoxicity	Vigfusson, N. V. and E. R. Vyse (1980). "The effect of the pesticides, Dexon, Captan and Roundup, on sister-chromatid exchanges in human lymphocytes in vitro." <i>Mutat Res</i> 79(1): 53-57.
Retracted Article	Séralini, G.-E., et al. (2014). "Retraction notice to "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" [<i>Food Chem. Toxicol.</i> 50 (2012) 4221–4231]." <i>Food and Chemical Toxicology</i> 63: 244.

Appendix B

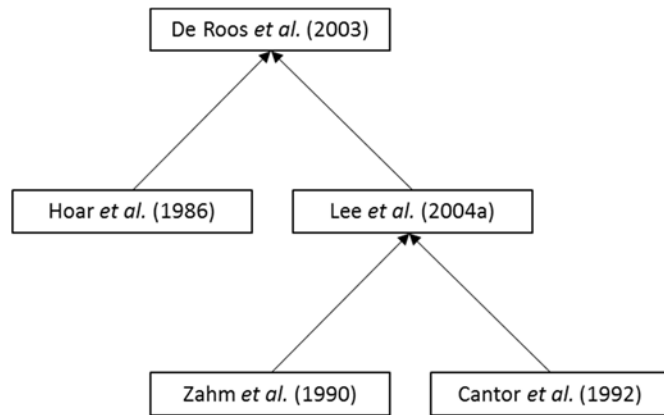


Figure B.1. Visual representation of studies included in De Roos *et al.* (2003).

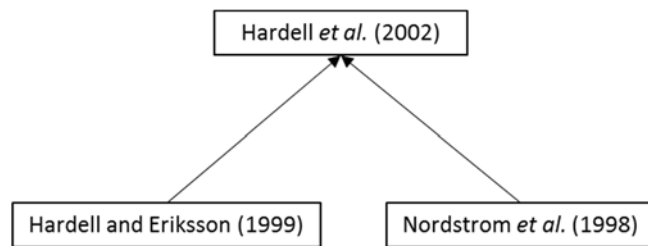


Figure B.2. Visual representation of studies included in Hardell *et al.* (2002).

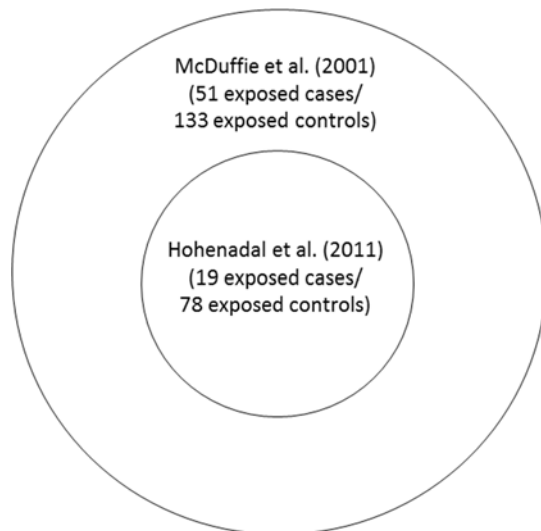


Figure B.3. Visual representation of the association between McDuffie *et al.* (2001) and the follow-up analysis by Hohenadal *et al.* (2011).

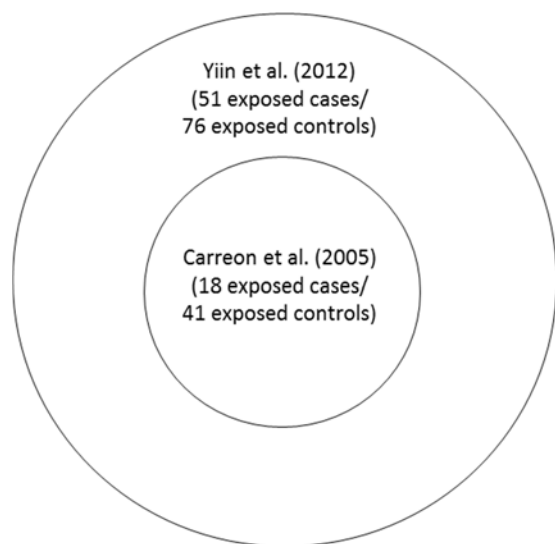


Figure B.4. Visual representation of the association between Carreon *et al.* (2005), which investigated gliomas in women only, and Yiin *et al.* (2012), which investigated both sexes.

Appendix C

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.

Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
Alavanja <i>et al.</i> (2003)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2001	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	566 cases 54,766 controls	not reported	No
Andreotti <i>et al.</i> (2009)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2004	Participants enrolled in AHS; licensed private and commercial applicators and spouses	Participants enrolled in AHS; licensed private and commercial applicators and spouses	93 cases (64 applicators, 29 spouses) 82,503 controls (52,721 applicators, 29,782 spouses)	55 cases 48,461 controls	No
Band <i>et al.</i> (2011)	Canada: British Columbia	1983-1990	Male residents in British Columbia identified as cancer patients in British Columbia Cancer Registry (excluding farmers that worked all outside British Columbia)	Male residents in British Columbia identified as cancer patients in British Columbia Cancer Registry (excluding farmers that worked all outside British Columbia) with other cancer sites excluding lung cancer and cancers of unknown primary site	1,153 cases 3,999 controls	25 cases 60 controls	Yes (included in adjustment)
Brown <i>et al.</i> (1990)	USA: Iowa and Minnesota	Iowa: 1981-1983; Minnesota: 1980-1982 Initial interview 1981-1984 and supplemental interviews (Iowa only) in 1987	White males (30 years or older) residing in Iowa or Minnesota diagnosed with leukemia	White males without lymphatic or hematopoietic cancer selected by random digit dialing (< age 65), Medicare records (age > 65) and state death certificate files (deceased controls) - frequency matched for 5-year age group, vital status, and state of residence	Initial: 578 cases; 1245 controls Supplemental: 92 cases; 211 controls	15 cases 49 controls	Yes (not evaluated)
Brown <i>et al.</i> (1993)	USA: Iowa	Iowa: 1981-1983; Interview 1981-1984	White males (30 years or older) residing in Iowa diagnosed with multiple myeloma	White males without lymphatic or hematopoietic cancer selected by random digit dialing (< age 65), Medicare records (age >	173 cases 650 controls	11 cases 40 controls	Yes (not evaluated)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
				65) and state death certificate files (deceased controls) - frequency matched for 5-year age group, vital status, and state of residence			
Cocco <i>et al.</i> (2013)	Czech Republic, France, Germany, Italy, Ireland, and Spain	1998-2004	Adult patients first diagnosed with lymphoma residing in the referral area of the participating centers	Controls from Germany and Italy were randomly selected by sampling from the general population, matched to cases on sex, 5-year age-group, and residence area. The rest of the centers used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases, and immunodeficient diseases	2,348 cases 2,462 controls	4 cases 2 controls	No
De Roos <i>et al.</i> (2003)	USA: Nebraska, Iowa, Minnesota, and Kansas	Nebraska: 1983-1986 Iowa: 1981-1983 Minnesota: 1980-1982 Kansas: 1979-1981	White males diagnosed with NHL in one of the 4 states (21 years or older in Nebraska and Kansas; 30 years or older in Iowa and Minnesota)	Males living in same geographic area obtained by random digit dialing. Medicare records and state mortality files - frequency matched for race, sex, age, and vital status	870 cases 2,569 controls	36 cases 61 controls	Yes (not significant in covariate analysis)
De Roos <i>et al.</i> (2005)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2001	Participants enrolled in AHS; licensed private and commercial applicators and spouses	Participants enrolled in AHS; licensed private and commercial applicators and spouses	54,315 subjects included in this analysis	All cancers – 358 cases Lung – 26 cases Oral cavity – 10 cases Colon – 15 cases Rectum – 14 cases Pancreas – 7 cases Kidney – 9 cases Bladder – 17 cases Prostate – 145 cases Melanoma – 14 cases All lymphohematopoietic cancers – 36 cases NHL – 17 cases Leukemia – 9 cases	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
						Multiple myeloma – 6 cases (13,280 subjects not exposed to glyphosate used for comparison population)	
Engel <i>et al.</i> (2005)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2000	Wives of applicators enrolled in AHS study with no history of breast cancer	Wives of applicators enrolled in AHS study with no history of breast cancer	309 cases 30,145 controls	82 cases; 10,016 controls	No
Eriksson <i>et al.</i> (2008)	Sweden	1999-2002	Patients (18-74 years of age) residing in Sweden and diagnosed with NHL	Swedish residents randomly selected living in same health service regions as cases - frequency matched for age (in 10 years) and sex	910 cases 1,016 controls	29 cases 18 controls	No
Flower <i>et al.</i> (2004)	USA: Iowa	1993-1997	Children (born after 1975) of participants enrolled in AHS study who were diagnosed with childhood cancer up to 19 years of age	Children (born after 1975) of participants enrolled in AHS study not diagnosed with childhood cancer up to 19 years of age	50 cases out of 17,357 total study population	Maternal use: 13 cases of 6075 total exposed Paternal use: 6 cases of 3231 total exposed	No
Hardell <i>et al.</i> (2002)	Sweden	NHL: 1987-1990 HCL: 1987-1992	NHL: Male residents of one of four northern or three middle counties in Sweden age 25 years and older diagnosed with NHL; identified from regional cancer registries HCL: Living male residents of Sweden age 25 years and older diagnosed with HCL; identified from the Swedish Cancer Registry	NHL: Two male controls for each case matched by age, year of death if deceased, and county HCL: Four male controls for each case matched by age and county	515 cases 1,141 controls	8 cases 8 controls	Yes (not evaluated)
Kachuri <i>et al.</i> (2013)	Canada: Alberta, British Columbia, Manitoba, Ontario,	1991–1994	Men aged ≥ 19 years (≥ 30 years in analysis) - pulled from hospital records in Quebec,	Men aged ≥ 19 years (30 years in analysis) - pulled from provincial health insurance records in	342 cases 1,357 controls	32 cases 121 controls	Yes (included in adjustment)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
	Quebec, and Saskatchewan		cancer registries in all other provinces	Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia			
Karunanayake <i>et al.</i> (2012)	Canada: Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	1991–1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	316 cases 1,506 controls	38 cases 133 controls	No
Koureas <i>et al.</i> (2014)	Greece	2010	Inhabitants of the city of Larissa; Eligibility criteria for pesticide sprayers were 1) to personally apply pesticides systematically, and 2) to have recently applied pesticides (no longer than 7 days between last application and sampling).	The rural residents group were occupied in administrative services, public order services, health services, education or trade. Inclusion criteria for this group: absence of any involvement in agricultural activities either as a primary or secondary occupation by participant or any member of household. Also recruited urban residents (mainly blood donors) from the city of Larissa.	80 pesticide sprayers, 85 rural residents, and 121 individuals	Not reported	No
Koutros <i>et al.</i> (2013)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2007	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	1,962 incident cases (including 919 aggressive prostate cancers) among 54,412 applicators	1464 cases 42,420 controls	No
Landgren <i>et al.</i> (2009)	USA: Iowa and North Carolina	Exposure information: enrollment (1993-1997) and 5-year follow-up interview	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	678 participants	27 cases out of 570 total exposed	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
		Blood samples: 2006-2007 (Iowa) and 2008 (North Carolina)					
Lee <i>et al.</i> (2004b)	USA: Nebraska	1988-1993	White residents of 1 of 66 Nebraska counties age 21 years or older with a newly confirmed case of adenocarcinoma of the stomach or Cases identified from the Nebraska Cancer Registry (1988–1990) or from discharge diagnosis and pathology records from 14 Nebraska hospitals (1991–1993)	Frequency matched by age and sex to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Health Care Financing Administration Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased)	Stomach: 170 cases Esophagus: 137 cases 502 Controls	12 cases 46 controls	Yes (analysis showed differences)
Lee <i>et al.</i> (2005)	USA: Nebraska	1988-1993	White residents of 1 of 66 Nebraska counties age 21 years or older with confirmed adult glioma. Cases identified from Nebraska Cancer Registry or from participating hospitals in Lincoln and Omaha, Nebraska	Frequency matched by age, sex, and vital status to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased), and 5-year age groups to the overall case distribution. Additional	251 glioma cases 498 controls	17 cases 32 controls	Yes (analysis showed differences, included in adjustment)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
				younger controls were brought into the study through random digit dialing and from death certificates			
Lee <i>et al.</i> (2007)	USA: Iowa and North Carolina	1993-97; follow-up to 2002	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of colorectal cancer at enrollment. Followed through 2002 for incident colorectal cancer	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of colorectal cancer at enrollment. Followed through 2002 for incident colorectal cancer	56,813 licensed pesticide applicators 305 incident colorectal cancer cases (212 colon, 93 rectum) 56,508 controls	Colon - 151 cases; 49 controls Rectum - 74 cases; 18 controls Colorectal - 225 cases; 67 controls	No
McDuffie <i>et al.</i> (2001)	Canada: Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	1991-1994	Male residents of six Canadian provinces age 19 years and older diagnosed with STS, HD, NHL, or MM; this study only evaluated those with NHL. Cases were identified from Canadian Cancer Registries; in Quebec, hospital ascertainment was used	Random control subject selection using Health Insurance records, computerized telephone listings, and voters' lists; males 19 years and older from same six Canadian provinces as cases matched by age (within 2 years)	517 cases 1506 controls	Univariate analysis: 51 cases; 133 controls (multivariate analysis also conducted - glyphosate exposed numbers not reported)	No
Orsi <i>et al.</i> (2009)	France	2000-2004	Men aged 20–75 years living in the catchment areas of the main hospitals in Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux, with no history of immunosuppression or taking immunosuppressant drugs. Cases ascertained from hospital records.	Patients from the same hospital catchment area as the cases. Patients were hospitalized for orthopedic or rheumatological conditions (89.3%), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue disease (1.8%), and infections (3.0%), excluding patients admitted for cancer or a disease directly related to	491 cases 456 controls	NHL: 12 cases 24 controls HL: 6 cases 15 controls Lymphoproliferative syndromes: 4 cases 18 controls Multiple myeloma: 5 cases; 18 controls Lymphoid neoplasms: 27 cases; 24 controls	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
				occupation, smoking, or alcohol abuse			
Pahwa <i>et al.</i> (2011)	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	1991-1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	342 cases 1,506 age/resident matched controls	32 cases 133 controls	No
Pahwa <i>et al.</i> (2012)	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	1991-1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	342 cases 1506 age/resident matched controls	32 cases 133 controls	No
Yiin <i>et al.</i> (2012)	USA: Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	1995-1997	Age 18–80 (at ascertainment or diagnosis in 1995 through January 1997) residing in counties where the largest population center had fewer than 250,000 residents. Referral by physicians or through state cancer registries with cases verified by histological evaluation.	Controls age 18–64 randomly selected from state driver's license/nondriver ID records, and those age 65–80 were selected from Health Care Financing Administration's (HCFA) Medicare data within 10-year age group strata, with the proportion/stratum determined by the age distribution of glioma cases in that state from 1992 to 1994. Controls were frequency-matched within a state but not by county of residence. Selected even if they had a self-reported history of cancer other than glioma.	798 glioma cases; 1,175 controls	12 cases 19 controls	Yes (analysis showed no differences)

Appendix D. List of studies assigned a low quality ranking and not evaluated in detail

As described in Section 3.2, if studies did not collect exposure information on glyphosate from all subjects, did not assess an outcome (e.g., biomonitoring studies), and/or did not provide a quantitative measure of an association between glyphosate and a cancer outcome, then these studies were assigned a low quality ranking and were not further evaluated in detail. These studies included the following 32 studies:

Acquavella *et al.* 2006; Andre *et al.*, 2007; Baker *et al.* 2005; Benedetti *et al.*, 2013; Bolognesi *et al.*, 2002; Bolognesi *et al.*, 2004; Bolognesi *et al.* 2009; Bortoli *et al.*, 2009; Costa *et al.*, 2006; Da Silva *et al.* 2014; Dennis *et al.* 2010; Firth *et al.* 2007; Gomez-Arroyo *et al.*, 2013; Gregio D'Arce *et al.*, 2000; El-Zaemey *et al.*, 2013; Fortes *et al.*, 2016; Fritschi *et al.*, 2005; Hernandez *et al.*, 2006; Kaufman *et al.* 2009; Khayat *et al.*, 2013; Lebailly *et al.*, 2003; Mandel *et al.* 2005; Martinez-Valenzuela *et al.*, 2009; Monge *et al.*, 2007; Pastor *et al.*, 2003; Paz-y Mino *et al.*, 2007; Paz-y Mino *et al.* 2011; Ruder *et al.* 2004; Shaham *et al.*, 2001; Silva Kahl *et al.* 2016; Simoniello *et al.*, 2008; Vlastos *et al.*, 2006.

Appendix E

Chronic Dietary Exposure

The agency uses Dietary Exposure Evaluation Model- Food Consumption Intake Database (DEEM-FCID; version 3.16), which incorporates consumption data from United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA; 2003-2008) to calculate potential chronic dietary exposures. In an unrefined chronic dietary analysis, several conservative assumptions are used to generate high end estimates of potential exposure. These assumptions include tolerance-level residues for all registered commodities, 100% crop treated, and drinking water values from a direct application to water scenario, as well as DEEM default processing factors. For glyphosate, the highest exposure value for any population subgroup in an unrefined chronic dietary analysis would be 0.23 mg/kg/day for children 1-2 years old (Table E.1; see T. Bloem, 30-NOV-2017, D429229 for DEEM inputs and results).

Table E.1. Chronic dietary exposure estimates	
Population Subgroup	Exposure (mg/kg/day)
General U.S. Population	0.089771
All Infants (< 1 year old)	0.138338
Children 1-2 years old	0.228379
Children 3-5 years old	0.212036
Children 6-12 years old	0.147749
Youth 13-19 years old	0.088362
Adults 20-49 years old	0.074650
Adults 50-99 years old	0.061258
Females 13-49 years old	0.069318

Post-application Incidental Oral and Dermal Exposure

Glyphosate has residential uses, including application to turf, which would result in the highest potential post-application exposures; therefore, there is potential for children to be exposed via incidental oral and dermal routes from playing on treated lawns. For this assessment, the agency evaluates exposures from hand-to-mouth behavior, object-to-mouth behavior, incidental soil ingestion, and dermal contact using the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment²⁹. Incidental oral exposures from hand-to-mouth, object-to-mouth, and incidental soil ingestion are considered inter-related and, therefore, not combined. To calculate high end estimates of exposures, the following is assumed according to the 2012 SOP to be health-protective: 1) maximum label rates are applied to the turf, 2) exposures are assumed to occur every day to the residue values on the day of application (i.e., no dissipation), and 3) individuals engage in post-application activities for the maximum amount of time represented by data for children spending time outdoors and not specifically engaged in activities

²⁹ Available: <http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>

on turf, when in actuality children do not spend all of their outdoor time on turf. The highest exposure from incidental oral scenarios using the maximum application rate for turf applications would be 0.16 mg/kg/day from hand-to-mouth behaviors by children (1 to <2 years old). Dermal post-application to children 1 to <2 years old would be 0.08 mg/kg/day.

Table E.2. Post-application Exposure Estimates for Application of Glyphosate to Turf ¹ .			
Lifestage	Post-application Exposure Scenario		Exposure (mg/kg/day)
Children 1 to <2 year old	Turf – sprays	Hand-to-Mouth	0.16
		Object-to-Mouth	0.005
		Incidental Soil Ingestion	0.0003
		Dermal (high contact activities)	0.08

¹ Based on Roundup® Weed & Grass Super Concentrate, EPA Reg. No. 71995-25.

Appendix F

Genotoxicity Studies with Glyphosate Based Formulations

While the focus of this analysis to determine the genotoxic potential of glyphosate, the agency has identified numerous studies conducted with glyphosate-based formulations that contain various concentrations of the glyphosate as well as other components of the end use products and are presented in Tables F.1-F.5.

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98 and TA100; <i>E. coli</i> WP2 <i>uvrA</i> pKM101 ± S9	1.6-5000 µg/plate ± S9 (plate incorporation)	ICIA 0224 57.6% in water	Negative ± S9	Callander (1988)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537; <i>E. coli</i> WP2P and <i>uvrA</i> ± S9	100-5000 µg/plate ± S9 plate incorporation & pre-incubation protocols	TMSC (tri-methyl-sulfonium chloride) 95% purity	Negative ± S9	Callander (1993)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	26, 43, 72, 120, 200 µg/plate	Glyphosate liquid formulation (480 g/L isopropylamine salt)	Negative ± S9	Camolesi (2009) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	26, 43, 72, 120, 200 µg/plate	MON 77280 equivalent of glyphosate acid: 495 g/L	Negative ± S9	Camolesi (2010)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	0.2-2000 µg/plate	MON 76190 53.2% glyphosate	Negative ± S9	Catoyra (2009) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100 and TA102± S9	2 µg/plate (toxic)	Perzocyd 10 SL formulation	Negative ± S9	Chruscielska <i>et al.</i> (2000)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102,	0.03-3.0 µL/plate	MON 8080 (87.6%)	Negative ± S9	Flowers (1981)	

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
	TA1535, and TA1537 ± S9					
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	3.16-1000 µg/plate	TROP M (Glyphosate 480); 35.84% purity based on acid, 48.46% pure based on IPA salt	Negative ± S9	Flügge (2010a) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	0.316-100	Glyphosate 757 g/kg granular formulation (76.1% monoammonium glyphosate salt)	Negative ± S9	Flügge (2010d) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100, and TA1535 ± S9	1-5000 µg/plate	Roundup WG 784 g/kg ammonium salt equivalent	Negative ± S9	Gava (1998)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537± S9	50-5000 µg/plate	Rodeo® (containing IPA salt and water only); 40% glyphosate (acid equivalent)	Negative ± S9	Kier <i>et al.</i> , (1992)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 ± S9	5-500 µg/plate (-S9)/ 15-1500 µg/plate (+S9)	MON 2139 (Roundup®) 31% Glyphosate (acid equivalent)	Negative ± S9	Kier <i>et al.</i> , (1992)	Cytotoxic at top concentrations
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 ± S9	5-500 µg/plate (-S9)/ 15-1500 µg/plate (+S9)	MON 14445 (Direct®); 75% Glyphosate (acid equivalent)	Negative ± S9	Kier <i>et al.</i> , (1992)	Cytotoxic at the top concentrations, occasionally at lower concentrations
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 ± S9	0.2-2000 µg/plate	MON 79672 (Roundup Ultramax); 74.7% monoammonium	Negative ± S9	Lope (2008) ¹	

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
			glyphosate salt; 68.2% glyphosate			
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98 and TA100 ± S9	0.617-50 µL/plate ± S9	SC-0224, 19.2% purity	Negative ± S9	Majeska (1982)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	TA strains: 10 - 5000 µg/plate (+S9); 3.33-3330 µg/plate (-S9); <i>E. coli</i> : 33.3-5000 µg/plate (+/- S9)	MON 78239 36.6% glyphosate (44.9% potassium salt of glyphosate)	Negative	Mecchi (2003a)	Increase in revertants seen in TA98 and TA1535 -S9 on first trial, not conc-dep; however no increase in revertants seen in repeat in those strains; overall negative.
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	TA strains: 3.33-3330 µg/plate (+S9); 1.0-1000 µg/plate (-S9); <i>E. coli</i> : 33.3-5000 µg/plate (+/- S9)	MON 78634 65.2% w/w glyphosate (71.8% w/w as monoammonium salt of glyphosate)	Negative	Mecchi (2003b)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	10 - 5000 µg/plate (+/-S9)	MON 79864 38.7% glyphosate acid (wt %)	Negative	Mecchi (2008a)	Inhibited growth seen at ≥2000 -S9
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	33.3-5000 µg/plate	MON 76313 30.9% glyphosate acid	Negative	Mecchi (2008b)	

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	10-5000 µg/plate (+/-S9)	MON 76171 31.1% glyphosate	Negative	Mecchi (2008c) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	10-5000 µg/plate (+/-S9)	MON 79991 71.6% glyphosate acid	Negative	Mecchi (2009a)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA 98, TA100, TA1535, TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	10-5000 µg/plate (+/-S9)	MON 76138 38.5% glyphosate	Negative	Mecchi (2009b) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100, and TA1535 ± S9	1-5000 µg/plate	MON 77280 646.4 g/L salt equivalent	Negative	Perina (1998)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98 and TA100 ± S9	0-1440 µg/plate (calculated as glyphosate IPA salt)	Roundup, 480 g/L glyphosate isopropylamine salt	Negative – S9, Equivocal +S9	Rank <i>et al.</i> (1993)	Stat significant increase at 360 µg/plate for TA98 (-S9) and 720 µg/plate for TA100 (+S9). Not significant at higher concentrations and were not replicated. Effects occurred at close to toxic levels.

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	500-5000 µg/plate;	495 g/L glyphosate isopropylamine salt; 371.0 g/L (equivalent of glyphosate acid)	Negative ± S9	Silvino (2011)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	1.5-5000 µg/plate	MON 8709 495 g/L glyphosate isopropylamine salt; 371.0 g/L (equivalent of glyphosate acid)	Negative ± S9	Silvino (2011)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537 ± S9	15-5000 µg/plate	MON 76313 468 g/L glyphosate isopropylamine salt (351 g/L glyphosate acid equivalent)	Negative ± S9	Silvino (2012)	Cytotoxic at 5000 µg/plate for some strains
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA97a, TA98, TA100 and TA1535 ± S9	1-5000 µg/plate	Glifos formulation (glyphosate isopropylammonium salt, Berol 907 and water)	Negative ± S9	Vargas (1996)	Cytotoxic at the two upper concentrations
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA102, TA1535, TA1537± S9	3.16-316 µg/plate	FSG 3090-H1 360 g/L	Negative ± S9	Uhde (2004) ¹	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100 ± S9	0.01-100 µg/plate	64% (glyphosate Isopropylammonium salt)	Negative ± S9	Wang <i>et al.</i> (1993)	
Bacterial Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535,	All strains: 33.3-5000 µg/plate	MON 78910 30.3% glyphosate acid	Negative ± S9	Xu (2006)	Cytotoxic ≥1000 µg/plate (-S9)

Table F.1. <i>In vitro</i> Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
	TA1537 and <i>E. coli</i> WP2 <i>uvrA</i> ± S9	(+S9); 10-3330 µg/plate (-S9)				

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

Table F.2. <i>In Vitro</i> Tests for Chromosome Damage in Mammalian Cells- Glyphosate Formulations						
Test/Endpoint	Test System	Concentrations	Test Material/ Concentration	Results	Reference	Comments
<i>In vitro</i> Chromosomal Aberration using fluorescent in situ hybridization (FISH)	Bovine lymphocytes (from two 6-8 month old calves) -whole chromosome (1) painting probe	28-1120 µM 24 h exposure	62% Isopropylamine salt of glyphosate (38% inert ingredients)	Negative.	Holeckova (2006)	Small but significant increase in polyploidy seen at 56µM No positive control reported.
<i>In vitro</i> Cytokinesis Block Micronucleus Assay (with FISH analysis)	TR146 cells (human- derived buccal epithelial cell line)	0, 10, 15 and 20 mg/L; 20 minute exposure.	Roundup Ultra Max (450 g/l glyphosate acid)	Positive Increase in MN at all test concentratio ns	Koller <i>et al.</i> (2012)	No apoptosis observed at any conc. Necrosis reported at 20 mg/L. Increase in NB and NPB seen at all concentrations

MI= mitotic index. FISH= fluorescent in situ hybridization, MN= micronuclei; NB= nuclear buds; NPB= nucleoplasmic bridges.

Table F.3. <i>In Vivo</i> Tests for Chromosomal Aberrations in Mammals- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Chromosomal Aberration	Swiss albino mice (males only) Vehicle: DMSO	Intraperitoneal injection; sampling 24, 48 and 72 h	0, 25 and 50 mg/kg (5/dose)	Roundup (>41% isopropylamine glyphosate)	Positive Increase in MN at all time points at both doses	Prasad <i>et al.</i> (2009)	Significant decrease in mitotic index seen at all doses and time points
Bone Marrow Chromosomal Aberration	C57BL mice (males only) Vehicle: water	Oral administration; sampling 6, 24, 48, 72, 96 and 120 h	0.05, 0.01, 0.5 and 1.0% (8/dose)	Roundup	Negative	Dimitrov <i>et al.</i> (2006)	
Bone Marrow Chromosomal Aberration	New Zealand white rabbits (males only) Vehicle:	Drinking water for 60 days	0, 750 ppm (5/dose)	Roundup	Positive	Helal and Moussa (2005)	

BM= bone marrow, SC= spermatocyte.

Table F.4. <i>In Vivo</i> Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss CD1 mice (males only)	Intraperitoneal injection; 2 injections of half the dosage of 135 mg/kg 24 h apart; sampling at 6 and 24 h	0, 450 mg/kg roundup, equiv. to 135 kg glyphosate (3/dose)	Roundup, 30.4% glyphosate	Positive	Bolognesi <i>et al.</i> (1997)	Stat significant increase in MN at 6 and 24 h
Bone Marrow Micronucleus Test	C3H mice (males only) Vehicle: water	Intraperitoneal Injection (single treatment); sampling after 24, 48 and 72 h	0, 90 mg/kg	Not reported	Negative	Chruscielska <i>et al.</i> (2000)	
Bone Marrow Micronucleus Test	Swiss mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 50, 100 and 200 mg/kg	480g/L Isopropyla mine salt of glyphosate	Negative	Grisolia (2002)	
Bone Marrow Micronucleus Test	CD-1 mice (males and females)	Intraperitoneal injection; sampling 24, 48 and 72 h	0, 140, 280, and 555 mg/kg	Roundup (31% glyphosate salt)	Negative	Kier (1992)	Some deaths observed at high dose (HD), ↓PCE/NCE ratio at HD at 48 h in males.
Bone Marrow Micronucleus Test	Swiss albino mice (males and females)	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 212.5, 425 and 637.5 mg/kg	MON 77280 646.4 g/L glyphosate salt equivalent	Negative	Monma (1998)	Doses tested corresponded to 25%, 50% and 75% LD50

Table F.4. <i>In Vivo</i> Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	NMRI-Bom mice	Intraperitoneal Injection (single treatment); sampling after 24 h	0, 133 and 200 mg/kg (4/sex/dose)	Roundup, 480 g glyphosate isopropylamine salt per liter	Negative	Rank <i>et al.</i> (1993)	BM toxicity indicated by %PCE decreased at 200 mg/kg
Bone Marrow Micronucleus Test	Swiss albino mice (males only) ² Vehicle: water	Oral gavage (two treatments, 24 h apart); sampled at 18 and 24 h after last dose	0, 2000 mg/kg	MON 8709494.7 g/L salt of isopropylamine (371.0 glyphosate acid)	Negative	Claro (2011)	OECD 474 Guideline No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	C57BL mice (males only) Vehicle: water	Oral administration; sampling 6, 24, 48, 72, 96 and 120 h	0.05, 0.01, 0.5 and 1.0% (1%=1080 mg/kg) (8/dose)	Roundup	Negative	Dimitrov <i>et al.</i> (2006)	Toxicity seen in 1.0% dose group
Bone Marrow Micronucleus Test	CrI:CD-1(ICR) BR mice (males only) ² Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78239 (36.6% glyphosate)	Negative	Erexson (2003a)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CrI:CD-1(ICR) BR mice (males only) ² Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78634 (65.2% glyphosate)	Negative	Erexson (2003b)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CrI:CD-1(ICR) BR mice (males only) ² Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78910 (30.3% glyphosate)	Negative	Erexson (2006)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.

Table F.4. <i>In Vivo</i> Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	TROP M (Glyphosate 480); 358.4 g/L glyphosate acid; 483.6 g/L IPA salt	Negative	Flügge (2010c) ¹	OECD Guideline 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Swiss mice (males only ²) Vehicle: water	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 2000 mg/kg (6/dose)	A17035A 289.7 g/L glyphosate	Negative	Negro Silva (2009) ¹	OECD Guideline 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Swiss mice (males only ²) Vehicle: water	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 2000 mg/kg (6/dose)	Glyphosate SL (499.35 g/L glyphosate)	Negative	Negro Silva (2011) ¹	OECD Guideline 474 No significant signs of toxicity observed in main study
Bone Marrow Micronucleus Test	Hsd:CD-1(ICR) mice (males only ²) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 79864 (38.7% glyphosate)	Negative #	Xu (2008a)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only ²) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76171 (31.1% glyphosate)	Negative	Xu (2008b)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only ²) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 79991 (71.6% glyphosate)	Negative	Xu (2009a)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.

Table F.4. <i>In Vivo</i> Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only ²) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76138 (38.5% glyphosate)	Negative	Xu (2009b) ¹	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Hsd:CD-1(ICR)BR mice (males only ²) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76313 (30.9% glyphosate)	Negative	Xu (2009c) ¹	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD rats (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	757 g/kg granular formulation (69.1% glyphosate acid)	Negative	Flügge (2010e) ¹	OECD Guideline 474 No significant signs of toxicity observed in main study

¹ Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

² Only males tested; report indicated that there was no difference between sexes seen in range finding study.

BM= bone marrow, CA= chromosomal aberrations, MN= micronucleated erythrocytes, NCE= normochromatic erythrocytes, PCE=polychromatic erythrocytes.

Table F.5. Other Assays for Detecting DNA Damage- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material/ Concentration	Results	Reference	Comments
Bacterial SOS Chromotest	<i>Escherichia coli</i> PQ37 strain	NA (<i>in vitro</i>)	0.25µg/sample	Roundup BIO formulation;	Positive	Raipulis <i>et al.</i> (2009)	
DNA Adducts ³²P-postlabeling	Swiss CD1 mice (males and females) Liver and kidney evaluated	Intraperitoneal injection	0, 400, 500 and 600 mg/kg, corresponding to 122, 152 and 182 mg/kg glyphosate salt	Roundup (30.4% isopropylammonium salt of glyphosate)	Positive (liver and kidney)	Peluso <i>et al.</i> (1998)	
DNA oxidative damage: 8-OHdG formation	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	900 mg/kg corresponding to 270 mg/kg glyphosate (3/dose)	900 mg/kg corresponding to 270 mg/kg glyphosate	Kidney: positive at 8 and 24 h Liver: negative	Bolognesi <i>et al.</i> (1997)	
Single-cell gel electrophoresis (SCGE) assays-COMET assay	TR146 cells (human-derived buccal epithelial cell line). Alkaline conditions	NA (<i>in vitro</i>)		Roundup Ultra Max (450 g/l glyphosate acid)	Induced DNA migration at >20 mg/L	Koller <i>et al.</i> (2012)	Also measured multiple cellular integrity parameters to assess cytotoxicity. Formulation was more toxic than technical. Significant increase in LDHe at all concentrations tested. Cytotoxic ≥ 60 mg/L
Sister Chromatid Exchange (SCE)	Bovine lymphocytes	NA (<i>in vitro</i>)	28 - 1112 µM; ±S9; sampling at 24 and 48 h	62% Isopropylamine salt of glyphosate	Positive	Sivikova & Dianovsky (2006)	

Table F.5. Other Assays for Detecting DNA Damage- Glyphosate Formulations.							
Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material/ Concentration	Results	Reference	Comments
Sister Chromatid Exchange (SCE)	Human lymphocytes (2 donors)	NA (<i>in vitro</i>)	250, 2500 and 25000 µg/mL	Roundup; Isopropylamine salt of glyphosate (purity not stated)	Stat. significant increase (p<0.001) at 250 µg/mL in both donors, and in one donor at 2500 µg/mL	Vigfusson and Vyse (1980)	No growth seen at highest concentration (25 mg/mL)
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (<i>in vitro</i>)	-S9: 0, 0.1 and 0.33 mg/mL; 72 h exposure	Roundup, 30.4% glyphosate	Positive	Bolognesi <i>et al.</i> (1997)	Stat significant increase in SCE/cell at ≥ 0.1 mg/mL
Alkaline elution assay- DNA single strand breaks	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	900 mg/kg corresponding to 270 mg/kg glyphosate (3/dose)	900 mg/kg corresponding to 270 mg/kg glyphosate	Positive (Increased elution rate) at 4 hours in liver and kidney At 24 h, returned to control levels	Bolognesi <i>et al.</i> (1997)	Return to control values at 24 h may indicate DNA repair or reflect rapid elimination of compound

h= hour, NA= not applicable, SCE= sister chromatid exchange, LDHe= extracellular lactate dehydrogenase

Appendix G

The following studies were considered during the systematic review, but were excluded from the analysis.

Amer S.M. et al (2006). In vitro and in vivo evaluation of the genotoxicity of the herbicide glyphosate in mice. Bulletin of the National Research Centre (Cairo) 31 (5): 427-446.

Aboukila, R.S. *et al.* (2014). Cytogenetic Study on the Effect of Bentazon and Glyphosate Herbicide on Mice. Alexandria Journal of Veterinary Sciences, 41: 95-101.

Majeska (1982d) MRID 00126616

Majeska (1982e) MRID 00126614

Majeska (1982f) MRID 00126615