CENTER FOR FOOD SAFETY

September 3, 2019

OPP Docket
Environmental Protection Agency
Agency Docket Center (EPA/DC)
(28221T)
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001
Email: http://www.regulations.gov

Re: Comments on Glyphosate Proposed Interim Registration Review Decision, 84 Fed. Reg. 19782 (May 6, 2019); Case No. 0178, Docket EPA-HQ-OPP-2009-0361.

To whom it may concern:

Center for Food Safety (CFS), on behalf of itself and its 950,000 members and supporters, submit these comments in response to the Environmental Protection Agency's (EPA) Glyphosate Proposed Interim Registration Review Decision in Case No. 0178. CFS is a public interest, nonprofit membership organization with offices in Washington, D.C., San Francisco, California, and Portland, Oregon. CFS's mission is to empower people, support farmers, and protect the earth from the harmful impacts of industrial agriculture. Through groundbreaking legal, scientific, and grassroots action, CFS protects and promotes the public's right to safe food and the environment. CFS has consistently supported comprehensive EPA review of registered pesticides and individual inert ingredients.

I. Background

Pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and EPA's regulations implementing FIFRA, EPA is currently in the process of reviewing the registration of glyphosate.[1] EPA opened the registration review docket for glyphosate via a notice published in the Federal Register on July 22, 2009.[2] On April 30, 2018, CFS submitted comments on EPA's draft risk assessments for registration review of glyphosate (CFS 2018), which we incorporate by reference. On May 6, 2019, EPA published a notice in the Federal Register, announcing the availability and soliciting public input on the draft human health and ecological risk assessments for glyphosate.[3] CFS submits the following comments concerning issues that EPA should consider in its human health and ecological risk assessments of glyphosate as part of the registration review process. Non-EPA documents cited in these comments that have not been submitted previously are also being submitted.

[1] *See* 40 C.F.R. Part 155, subpart C.
[2] 74 Fed. Reg. 36217 (July 22, 2009).
[3] 84 Fed. Reg. 19782 (May 6, 2019).

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II. Relevant Legal Standards

A. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

Under FIFRA, EPA licenses the sale, distribution, and use of pesticides, including herbicides, through the process of registration.[4] EPA can register a pesticide only upon determining that "it will perform its intended function without unreasonable adverse effect on the environment,"[5] and that "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[6] FIFRA defines "unreasonable adverse effects on the environment" as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."[7]

FIFRA's registration review process is mandated at 7 U.S.C. § 136a(g). FIFRA requires that pesticide registrations are periodically reviewed, and that EPA "shall by regulation establish a procedure for accomplishing the periodic review of registrations."[8] EPA adopted regulations pursuant to this provision in 2006, which state that each pesticide is required to be reviewed every 15 years.[9] Registration review is intended to ensure that each active ingredient's registration is based on current science, including its effects on human health and the environment. If a product "fails to satisfy the FIFRA standard for registration, the product's registration may be subject to cancellation or other remedies under FIFRA."[10]

B. Federal Food, Drug, and Cosmetic Act (FFDCA)

The FFDCA[11] prohibits the introduction of "adulterated" food into interstate commerce.[12] The Act requires that where use of a pesticide will result in any pesticide residue being left on food, EPA must either set a "tolerance" level for the amount of allowable pesticide residue that

[4] 7 U.S.C. § 136a(5)(D).
[5] *Id*. § 136a(c)(5)(C).
[6] *Id*. § 136a(c)(5)(D).
[7] *Id*. § 136(bb).
[8] *Id*. § 136a(g)(1)(A).
[9] 40 C.F.R. §§ 155.40-155.58.
[10] *Id*. § 155.40(a).
[11] 21 U.S.C. § 301 *et seq.*
[12] 21 US.C. § 331.

can be left on the food, or set an exemption of the tolerance requirement.[13] The tolerance or exemption requirements apply to raw agricultural commodities such as MON 87708 soybean.[14]

The FFDCA mandates EPA to "establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the EPA Administrator determines that the tolerance is safe."[15] For a tolerance level to be "safe," the statute requires EPA determine "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[16] "Aggregate exposure" includes not only dietary exposure through food consumption, but also includes "exposures through water and residential uses."[17]

C. Food Quality Protection Act

In 1996, Congress passed the Food Quality Protection Act (FQPA), which amended FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA). When determining the safety of a pesticide chemical under the FQPA, EPA "shall base its assessment of the risk posed by the pesticide chemical on *aggregate* (i.e., total food, drinking water, residential, and other nonoccupational) exposure to the pesticide." EPA, *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity*, at 5 (Jan. 14, 2002) (emphasis in original); *see* 21 U.S.C. § 346a(b)(2)(A)(ii). "EPA is also required to consider available information concerning the *combined* toxic effects to human health that may result from dietary, residential, or other nonoccupational exposure to chemicals that have a common mechanism of toxicity." *Id*. (emphasis in original); *see* 21 U.S.C. § 346a(b)(2)(D)(v).

D. EPA's Duties Under the Endangered Species Act

The ESA requires EPA, in consultation with the U.S. Fish and Wildlife Service (FWS) or the National Marine Fisheries Service (NMFS), to ensure that any actions by the agency, here including, but not limited to, completing Registration Review for glyphosate, are not likely to jeopardize the continued existence of any threatened or endangered species, or result in the destruction or adverse modification of the critical habitat of such species.[18] For each federal action, EPA must request information from FWS and NMFS indicating whether any listed or proposed species may be present in the area of the agency action.[19] If listed or proposed species

[13] 21 U.S.C. § 346a(1).
[14] 21 U.S.C. § 321(r) defines "raw agricultural commodities" as "any food in its raw or natural state, including all fruits that are washed, colored or otherwise treated in their unpeeled natural form prior to marketing."
[15] 21 U.S.C. § 342(a)(2)(A) (emphasis added); *see also* 40 C.F.R. § 180.1(f).
[16] 21 U.S.C. § 346(a)(2)(A)(ii).
[17] *Natural Res. Def. Council v. Whitman*, No. C 99-03701-WHA, 2001 WL 1221774 (N.D. Cal. Nov. 7, 2001).
[18] 16 U.S.C. § 1536(a)(2).
[19] 16 U.S.C. § 1536(c)(1); 50 C.F.R. § 402.12.

may be present, EPA must prepare a "biological assessment" to determine whether the listed species may be affected by the proposed action.[20]

If EPA determines that its proposed action may affect any listed species or critical habitat, the agency must engage in formal consultation with FWS and/or NMFS. Effects determinations are based on the direct, indirect, and cumulative effects of the action when added to the environmental baseline and other interrelated and interdependent actions.[21] An agency is required to review its actions "at the earliest possible time" to determine whether the action may affect listed species or critical habitat.[22] Because EPA retains ongoing discretionary authority to modify the terms and conditions of its approvals, the agency's continuing authority over pesticide registrations constitutes an ongoing agency action and it has a continuing obligation to follow the requirements of the ESA.

To complete formal consultation, FWS/NMFS must provide EPA with a "biological opinion" explaining how the proposed action will affect the listed species or habitat.[23] If FWS/NFMS concludes the proposed action will jeopardize the continued existence of a listed species, the biological opinion must outline "reasonable and prudent alternatives."[24] If the biological opinion concludes the action is not likely to jeopardize the continued existence of a listed species, and it will not result in the destruction or adverse modification of critical habitat, FWS/NMFS must provide an incidental "take" statement specifying the impact of such incidental taking on the listed species and any "reasonable and prudent measures" that FWS/NMFS consider necessary or appropriate to minimize such impact, and also setting forth the "terms and conditions" that must be complied with by EPA to implement those measures.[25]

During consultation with FWS/NMFS, EPA is prohibited from making any irreversible or irretrievable commitment of resources with respect to the agency action which may foreclose the formulation or implementation of any reasonable and prudent alternative measures.[26] ESA Section 7 also requires EPA, in consultation with and with the assistance of FWS/NMFS, to utilize its authority in furtherance of the purposes of the ESA by carrying out programs for the conservation of endangered and threatened species.[27]

III. Purpose of Registration Review

EPA is undertaking a registration review of glyphosate. Mandated byFIFRA, the purpose of the registration review program is to provide EPA with an opportunity to periodically (every 15 years) assess the risks that a pesticide may pose to human health and the environment in the

[20] *Id*.
[21] 50 C.F.R. § 402.02.
[22] 50 C.F.R. § 402.14(a).
[23] 16 U.S.C. § 1536(b).
[24] *Id*. § 1536(b)(3)(A).
[25] *Id*. § 1536(b)(4).
[26] 16 U.S.C. § 1536(d).
[27] 16 U.S.C. § 1536(a)(1).

light of new scientific information, enhanced ability to detect risks, changes in pesticide policy, and alterations in pesticide usage practices, since the pesticide was last registered.[28]

The EPA first registered glyphosate Case #0178, in 1974. Summary, p. 5. Since then, several genetically engineered crops modified specifically to withstand direct application of glyphosate have been deregulated by the U.S. Department of Agriculture. Commercially-grown glyphosate-resistant crops include corn, cotton and soybeans.

The EPA has made several regulatory decisions to facilitate the cultivation of glyphosate-resistant crops, for instance, approving new tolerances for glyphosate residues in or on glyphosate-resistant varieties of the crops noted above under the Federal Food, Drug and Cosmetic Act.[29] Yet none of these decisions has addressed the serious issues raised by the significantly altered use pattern of glyphosate as used with glyphosate-resistant crops, either individually or cumulatively. These issues include the following:

1) Greatly increased use of glyphosate as a cumulative impact of increasing cultivation of glyphosate-resistant crops;
2) Radically altered use pattern from use primarily in orchards, to post-emergence use in major field crops, such as corn, soybeans and cotton;
3) Accelerated evolution of glyphosate-resistant weeds from increased use and post-emergence use pattern; and
4) More damage to neighboring crops and non-target organisms from increased use and post-emergence use pattern.

A registration review is the proper venue for considering these issues. EPA is now ten years into the glyphosate registration review process yet the Agency has not even provided an assessment of changing glyphosate use patterns in light of the rapidly increasing acreage planted to glyphosate-resistant crops, the prerequisite to a sound treatment of "crop resistance" issues. The summary document barely mentions glyphosate-resistant crops, and where it does, only in the context of eliminating any distinction between transgenic and non-transgenic crops for the purposes of tolerance expressions. Neither SLUA nor BEAD mentions glyphosate-resistant crops, or takes account of their sharply increasing acreage for the purposes of the usage estimates. CFS likewise found no consideration given to adverse impacts on the environment that would result from increased prevalence of glyphosate- and multiple herbicide-resistant weeds fostered by post-emergence glyphosate use on glyphosate-resistant crops; or from increased prevalence of glyphosate- and multiple herbicide-resistant crop volunteers acting as weeds.

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[28] *See* EPA, *Registration Review Process*, https://www.epa.gov/pesticide-reevaluation/registration-review-process.

[29] *See* FDA, *Questions and Answers on Glyphosate*, https://www.fda.gov/food/pesticides/questions-and-answers-glyphosate ("EPA has established tolerances for glyphosate on a wide variety of crops, including corn, soybean, oil seeds, grains, and some fruits and vegetables, ranging from 0.1 to 310 ppm.").

Registration reviews are supposed to account for changing use patterns, not ignore them. On its present course, EPA will complete the registration review of glyphosate with conclusions and registration actions that are based on yesterday's usage patterns. Such registration actions would likely be outdated before they are even taken, and they would be very unlikely to account for some of the risks posed by glyphosate's use. Basing a registration review on vastly underestimated usage and outdated use patterns would also represent a tremendous waste of Agency resources, since registration reviews require on the order of five years and substantial Agency resources.

Therefore, CFS urges EPA to revise its assessment of glyphosate use patterns along the lines indicated below, and revise its risk assessments accordingly.

IV. EPA cannot proceed to a final decision without first providing the public a complete proposed decision and soliciting additional public comment.

Under its registration review procedures, EPA "may issue, when it determines it to be appropriate, an interim registration review decision before completing a registration review."[30] According to EPA, following the close of the current 60-day comment period, if EPA does not make any changes to the PID, it "may issue an interim registration review decision for glyphosate."[31] However, EPA also states that "a final decision for glyphosate may be issued without the agency having previously issued an interim decision."[32] In other words, EPA claims that it can proceed directly from a "proposed interim decision" to a final decision without any other opportunity for public comment. This undermines the public commenting process because, as EPA itself acknowledges, the PID lacks significant information about endangered species, pollinators, and endocrine disruption.[33]

EPA can register a pesticide only upon determining that "it will perform its intended function without unreasonable adverse effects on the environment,"[34] and that "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[35] Through registration review, EPA must "ensure that each pesticide registration continues to satisfy the FIFRA registration standard."[36] This requires that "each pesticide's registration is based on current scientific and other knowledge regarding the pesticide, including its effects on human health and the environment."[37]

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[30] 40 C.F.R. § 155.56.
[31] PID at 40.
[32] *Id*.
[33] *Id*. ("EPA is making no human health or environmental safety findings associated with the EDSP screening for glyphosate, not is it making a complete endangered species finding or a complete assessment of effects to pollinators.").
[34] 7 U.S.C. § 136a(c)(5)(C).
[35] *Id*. § 136a(c)(5)(D).
[36] 40 C.F.R. § 155.40(a).
[37] *Id*. § 155.40(a)(1).

It is essential that EPA disclose to the public in a timely manner the "current scientific and other knowledge regarding the pesticide" so that members of the public can make informed comments.[38] EPA cannot abuse the registration review process by forcing the public to comment on a woefully incomplete PID only to proceed to a final decision once the missing data is supplied but without any further opportunities for public comment.

It is also inconsistent with EPA's regulations. For example, according to EPA's regulations, "[a]mong 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*."[39] As stated above, EPA acknowledges that the PID is missing critical information on endangered species, pollinators, and endocrine disruption that the public has a right to see and comment on *before* EPA "complet[es] the registration review." In addition, 40 C.F.R. 155.58(b)(3) provides that when additional data is needed, as it is here, a notice requiring such data may be issued "in conjunction with a proposed or final decision on the registration review case *or a proposed **or final** interim decision* on a registration review case." Thus, the regulations specifically contemplate that a "final interim decision" follows the "proposed interim decision" rather than moving straight to a "final decision" on registration review as EPA suggests it can do.

V. Introduction

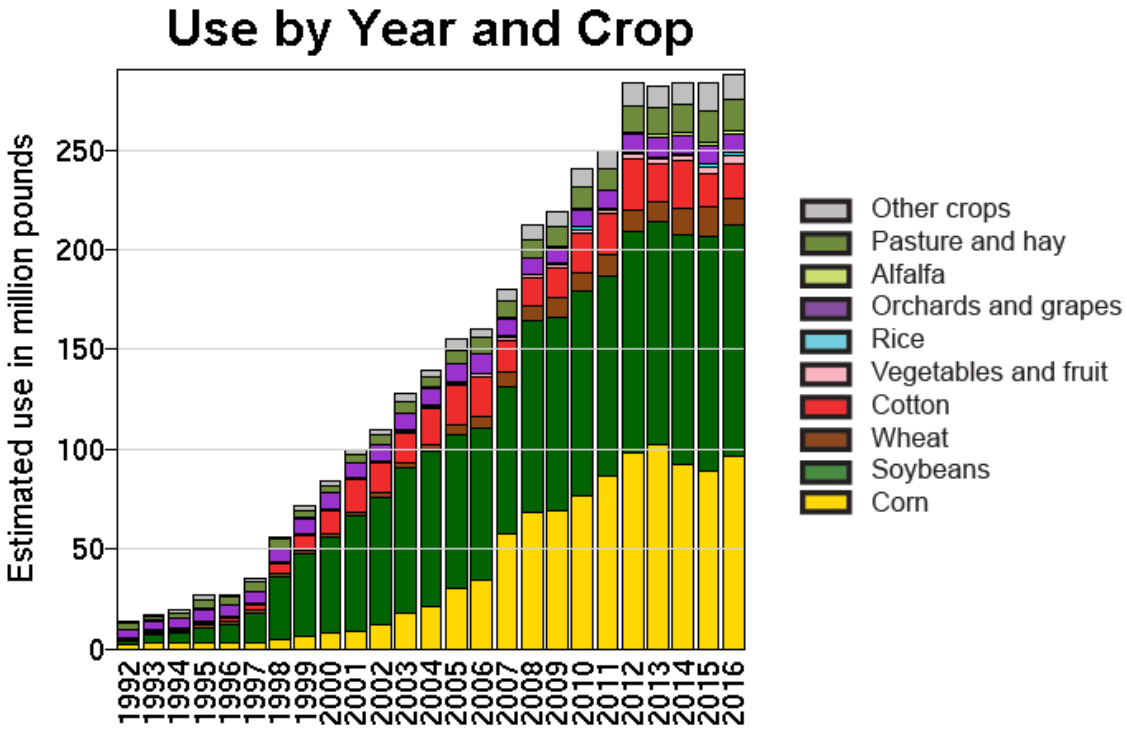
Glyphosate is the most intensively and extensively used conventional pesticide in the United States. EPA estimates that 280 million lbs. of glyphosate are applied to 298 million acres annually in agriculture, and an additional 24 millions lbs. per year in non-crop settings (EPA 4/18/19, pp. 13, 17). The U.S. Geological Survey provides a similar estimate for agricultural use of glyphosate (see graph below). Agricultural use of glyphosate is thus four times that of the second-leading conventional pesticide, atrazine (EPA 2017, Table 3.4).

Glyphosate's excessive use – driven primarily by the widespread planting of crops resistant to the herbicide (and increasingly to additional herbicides) – has had many serious adverse impacts on the environment, U.S. agriculture and the health of farmers and the general public. CFS predicted many of these harms ten years ago in comments on EPA's scoping documents for the registration review (CFS 2009). The herbicide's broad-scale use means that far more people and organisms are exposed to it than to lesser-used pesticides, arguing for

[38] *Ohio Valley Envtl. Coal. v. U.S. Army Corps of Eng'rs*, 674 F.Supp.2d 783, 808 (S.D.W.V. 2010) (absence of substantive information in agency notice "shielded essential data and detail from public review and comment and prevented the public from commenting intelligently on the adverse impacts[.]").
[39] 40 C.F.R. § 155.56 (emphasis added).

careful and conservative assessments to protect human and ecological health. EPA must take action to ameliorate these impacts through prudent usage restrictions, as needed.

By many measures, U.S. agriculture is becoming ever more addicted to weedkillers – both glyphosate and increasingly other herbicides. Agricultural glyphosate use has increased roughly 10-fold since the introduction of glyphosate-resistant crops in the mid-1990s. By one estimate, the widespread planting of glyphosate-resistant corn, soybeans and cotton has increased overall herbicide use by 527 million pounds, cumulatively, over what it would have been otherwise in the 16 years from 1996 to 2011 (Benbrook 2012). Agricultural herbicide use has accelerated in recent years, increasing from 420 million lbs. in 2005 to 564 million lbs. in 2012, a massive 34% rise in just seven years (EPA 2017, Table 3.2).



Source: US Geological Survey, Pesticide National Synthesis Project, last accessed 8/28/19. https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2016&map=GLYPHOSATE&hilo=L.

And it is not only the gross volume of herbicide that is increasing, it is also the number of herbicide applications made to the typical acre. For instance, data from USDA's National Agricultural Statistics Service show that the typical acre of corn receives fully twice as many

herbicide applications as it did in 1990.[40] Seventy-three (73) herbicidal active ingredients were applied to U.S. corn in 2014.[41]

U.S. agriculture's glyphosate addiction has spawned an epidemic of glyphosate-resistant weeds on roughly 120 million acres of U.S. cropland (Pucci 2018). The unsustainable "fixes" are an expanding suite of new genetically engineered crops resistant to both glyphosate and one or more other toxic herbicides, such as dicamba, 2,4-D, glufosinate and isoxaflutole, with many more awaiting approval or in development. None of the increase figures cited above reflect the further spiraling intensification of herbicide use and weed resistance these new GE crops – only now being introduced at scale – are already beginning to trigger, as many predicted they would (Mortensen et al. 2012, Keim 2015).

Herbicides must be viewed in the larger context of agricultural chemical use, given the potential for adverse impacts from additive or synergistic effects. In 2013, U.S. Geological Survey scientists tested 100 Midwestern streams for a range of pesticides (insecticides and fungicides as well as herbicides), and detected 94 pesticides and 89 degradates, with an astonishing median of 25 compounds detected per sample. Their study documented "the most complex pesticide mixtures yet reported in discrete water samples in the U.S.," and predicted potentially toxic effects to nontarget aquatic life in about half of the sampled streams (Nowell et al. 2018).

VI. Neither Peer-Reviewed Literaure Nor Comments Influenced EPA's Risk Assessments

EPA received 238,290 comments on its preliminary risk assessments of glyphosate, including roughly 2,244 unique submissions, many of which provided nuanced scientific critiques. Yet none of the comments resulted in changes to EPA's risk assessments (EPA 2019, pp. 6-7). As we pointed out in our 2018 comments, neither did EPA make any use of the 1,271 glyphosate toxicity studies in its ECOTOX database, nor the additional 609 peer-reviewed studies acceptable for both ECOTOX and the Office of Pesticide Programs, in the quantitative estimate of ecological risk (EPA Bibliography undated). Peer-reviewed literature also did not have any impact on EPA's human health risk assessment of glyphosate (EPA 4/23/18, p. 4) or in particular the evaluation of glyphosate's carcinogenic potential (EPA 2019, p. 9).

[40] From an average of 2.0 acre-treatments in 1990 to 4.0 acre-treatments in 2016. Source: USDA NASS Agricultural Chemical Use Surveys for the respective years. The acre-treatment metric represents the number of active ingredient applications to a typical crop acre in a single year. For instance, 4 acre-treatments might represent four applications of herbicide products, each of which contain one herbicide active ingredient (a.i.), or two applications of dual-a.i. herbicide mixes, etc.

[41] Source: USDA NASS Agricultural Chemical Use Survey. Count includes multiple versions of several herbicides, primarily glyphosate, 2,4-D and dicamba.

EPA's dismissal of informed comments and independent scientific studies that undergo peer review on mostly spurious grounds in favor of industry studies where conflicts of interest present obvious motivations for for bias and fraud is unacceptable (Rohr and McCoy 2010). EPA relies heavily on the use of Good Laboratory Practices (GLP) as a false marker of scientific quality, yet GLP standards are mostly procedural and record-keeping requirements that were first instituted by federal agencies in response to massive fraud on the part of private testing firms conducting studies on behalf of corporate clients seeking regulatory approval of their products (Myers et al. 2009). GLP does not ensure scientific quality; peer review of studies by independent scientists is a far better guarantor.

A 2012 Scientific Advisory Panel on atrazine took EPA to task for the excessively stringent criteria it applied in screening out peer-reviewed studies: "In the view of the Panel, the test design elements should not be applied so strictly to the published literature as to disqualify all studies that do not meet all of these criteria... In the Panel's analysis, the EPA's strict application of the test design elements to the published literature was flawed and many of the test design elements should be relaxed for review of the published literature." The Panel also stressed that such independent studies could be "very useful in risk assessment (even quantititative assessment), even if some of these design elements are not met" (SAP 2012, pp. 15, 30). The same of course is true of EPA's risk assessment of glyphosate.

VII. Glyphosate Formulations With POEAs and Other Surfactants

In our 2018 comments, CFS criticized EPA's failure to provide any meaningful assessment of the human health and ecological hazards posed by glyphosate formulations, which contain undisclosed "inert" ingredients in addition to glyphosate. Among these ingredients are surfactants, which facilitate greater absorption of glyphosate into plant tissues, increasing its weed-killing efficacy. Surfactants and other inerts represent the "black box" of industrial agriculture – jealously guarded as trade secrets by pesticide companies. They are not disclosed on the pesticide label, and only EPA is informed of their identity (Cox and Surgan 2006).

The EPA singles out one class of surfactants used in many glyphosate formulations as being of particular concern due to their known toxicity: polyethoxylated tallow amines (POEAs). In the Preliminary Ecological Risk Assessment, EPA assumes that POEAs are essentially the only surfactants that are toxic to aquatic organisms, and builds its entire exposure and risk assessment strategies on this overly simplistic foundational assumption (EPA 9/8/15, pp. 19, 62). Yet at the start of the registration review process, EPA revealed much less certainty, stating: Formulations with POEA "tend to be" the most toxic to aquatic organisms; but that "[o]nly a few" toxicology studies have been conducted with formulations containing surfactants other than POEA; "[f]or most formulations, we have no data"; "there are some non-POEA formulations that appear to be quite a bit more toxic than" glyphosate alone (EPA 6/5/09, p. 19). EPA also

conceded "uncertainty" about whether or not some aquatic use formulations "contain POEA-type surfactants" or others more toxic than glyphosate alone, resulting in "considerable uncertainty about the risk to aquatic organisms" (Ibid, pp. 19, 31). In light of the data gaps and uncertainty, it is entirely possible that some non-POEA glyphosate formulations are even more environmentally toxic than those with POEA. This is also true with respect to human health.

> Experimental studies suggest that the toxicity of the surfactant, polyoxyethyleneamine (POEA), is greater than the toxicity of glyphosate alone and commercial formulations alone. There is insufficient evidence to conclude that glyphosate preparations containing POEA are more toxic than those containing alternative surfactants" (Bradberry et al. 2004).

While Bradberry et al. dealt specifically with acute exposure to glyphosate formulations, the same is true of chronic exposure.

EPA admitted that it had not even identified the surfactants in many glyphosate formulations: "There are many formulated products for glyphosate and the surfactants used in these products that [sic] must first be identified" (EPA 6/5/09, p. 31). EPA was still scrambling to gather this basic formulation information seven years later (Gillam 2017). In 2016, EPA Chemical Review Manager Khue Nguyen emailed Monsanto executives with a "time sensitive" information request (EPA 4/6/16). In the notes attached to that email, regarding a meeting held the previous day between EPA and Monsanto, she stated:

> "In an effort to resolve questions about the potential toxicity of glyphosate, glyphosate formulations, and any co-formulants (inert ingredients and surfactants), EPA was interested in any data or information Monsanto may have on how the formulations may differ from data on the active ingredient and surfactants independently of one another …. Monsanto indicated that up until 2000, nearly all glyphosate products on the market were its Roundup formulation which used some form of tallow amine as a surfactant. Afterwards, the properties of surfactants used and the ratio of surfactant to active ingredient were changed in most formulations... EPA suggested that Monsanto provide in writing any information that documents the changes of glyphosate formulations over time and across the globe" (EPA 4/5/16).

EPA has had ten years to gather compositional and toxicity data on the 555 glyphosate-containing products on the U.S. market, but continues to treat such information as optional, to be used only if it happens to be available in registrant studies. EPA provided no assessment of any glyphosate formulation containing surfactants other than POEA because it has not demanded corresponding data from registrants (EPA 11/21/18, pp. 2-3).

The scope of this problem is suggested by a patent issued to Monsanto in 2010, Novel Surfactants and Formulations (Monsanto 2010). In this patent, Monsanto tests the weed-killing efficacy of glyphosate formulations containing 1 to combinations of 2 or 3 of 166 different proprietary excipients (additional formulation ingredients comprising mainly surfactants but also solublizers and other inerts) (Ibid., pars. 0407 to 0613). The hundreds to thousands of different glyphosate formulations used in this testing give a sense of the tremendous range of possibilities in commercial glyphosate products, products for which EPA has next to no toxicity data for either human health or ecological risks.

In response to formulation concerns, EPA stated that it evaluates the hazard potential of "inert ingredients" (including surfactants) with a "battery of toxicity data" (EPA 2019, p. 10). As an initial matter, separate data on inerts alone are no substitute for formulation toxicity testing, since inerts are designed to enhance efficacy against the target pest (e.g. weed), and so might well enhance adverse non-target effects as well.

Even with respect to the toxicity of inerts by themselves, the data that EPA collects is entirely inadequate in several critical respects, and cannot ensure their safety. First, EPA does not specify a required data set for inert ingredients, making the inerts assessment process an ***ad hoc*** affair (EPA 5/6/14). Second, EPA often approves entire classes of inert compounds, based on toxicity data for just a few. Third, EPA usually exempts classes of inerts from the requirement of a tolerance, meaning there are no limits to the amounts permissible as residues on foods (EPA 5/6/14). Finally, EPA collects far less data for inerts than for active ingredients, and to fill data gaps relies on "surrogate information" for other similar compounds, and *in silica* modeling to guestimate toxicity based on "structure-activity" relationships. These issues are discussed further below.

VIII. Glyphosate and Human Health

A. Chronic toxicity of glyphosate

Over the past 40+ years, EPA has facilitated wider and more intensive use of glyphosate by approving ever more "tolerances" – or maximum permitted residue levels of glyphosate – on a steadily expanding array of food crops and raw agricultural commodities (compare lists at EPA 3/3/83, pp. 4-5 to EPA 12/12/17, Table C.2, pp. 36-39). These allowable levels have also been increased dramatically on particular crops, such as wheat and oats. With rising tolerances came greater exposure to glyphosate in food. Below, we discuss how EPA has dramatically increased the level of glyphosate exposure it regards as safe to accommodate expanding use of the herbicide and greater amounts in the food supply.

EPA sets the threshold for "safe" long-term exposure by assessing studies in which groups of experimental animals, usually rats, are fed different doses of the chemical, here

glyphosate, on a daily basis for up to two years. For each study, the lowest dose found to cause an adverse effect attributable to the chemical, and the highest that does not, are identified: the lowest observed adverse effect level (LOAEL) and the no observed adverse effect level (NOAEL). EPA then selects, from among the well-conducted studies relevant to the endpoint (here, chronic toxicity), the one in which animals show compound-related effects at the lowest dose. The NOAEL from that study is then used to derive the chronic reference dose, the maximum level of exposure deemed safe for humans (EPA 1993a). Normally, the NOAEL is divided by two 10x safety factors: one to account for potentially greater susceptibility of human beings versus the experimental animal, and a second 10x factor to account for differences in susceptibility in the human population. The following discussion describes how, over time, EPA has repeatedly shifted its choice of the critical study to those which justify higher "safe" lifetime exposure levels. It is based on EPA memoranda and toxicological evaluations released in response to a Freedom of Information Act request.

The chronic reference dose (cRfD, formerly called "acceptable daily intake" or ADI) from roughly 1978 to the early 1980s was 0.05 mg/kg bw/day. This means that the maximum level of daily exposure to glyphosate regarded as safe was 0.05 milligrams per kilogram body weight, which translates to 3 milligrams glyphosate per day for a typical 60 kilogram adult (60 x 0.05), or 0.5 mg for a 10 kilo child. This cRfD was based on a two-year feeding study in which glyphosate fed to rats in the high-dose group was found to induce an increase in lipid levels in the the animals' liver cells (EPA 8/21/78). The next-lower dosage group of 5 mg/kg bw/day, in which rats did not exhibit this effect, was identified as the NOAEL. Application of the two standard 10x safety factors yielded the cRfD of 0.05 mg/kg bw/day (EPA 12/11/78). Accumulation of excessive fat in liver cells leads to nonalcoholic fatty liver disease, "the most important cause of chronic liver disease worldwide," which is associated with obesity, type 2 diabetes and dyslipidemia (Nassir et al. 2015).

In a three-generation rat reproduction study, 2nd and 3rd generation offspring fed the highest glyphosate dose "exhibited reduced mating, fertility and pregnancy indices" (EPA 2/16/77, p. 3). This study also supported a cRfD of 0.05 mg/kg bw/day (Ibid., EPA 8/14/78).

In 1982, EPA doubled the cRfD to 0.1 mg/kg bw/day by choosing a second three-generation rat study on which to base its cRfD, in which third generation rats exhibited renal tubular dilation (EPA 7/21/82). This study was regarded as high-quality, and served as the basis for the cRfD for a decade.

Then, in 1993, EPA raised the cRfD to 2.0 mg/kg bw/day – a massive 20-fold increase. This significant action was taken on the basis of a deeply flawed developmental study in which 10 of 16 rabbits in the high-dose group (350 mg/kg/day) died. It should have been rejected, but EPA instead identified the next lower dose (175 mg/kg/day) as the NOAEL, and used this

NOAEL as the benchmark for a new cRfD of 2.0 mg/kg bw/day (EPA 1/15/93, pdf pp. 8-9, 11), lowered a few years later to 1.75 mg/kg bw/day.[42] A study so deficient that it should have been rejected out of hand instead became the "critical study" that defined the "safe" level of exposure to glyphosate for a quarter of a century.

EPA has proposed a new cRfD of 1.0 mg/kg bw/day in the current registration review process. This is based on a 1996 rabbit developmental toxicity study very similar to the one described above, employing the same doses of glyphosate. The NOAEL of 100 mg/kg bw/day was established based on the observation of "diarrhea and few and/or no feces" in maternal rabbits of the next-higher dose (EPA 12/12/17, p. 16).

The low-dose adverse effects discussed above – lipid accumulation in liver cells; reduced mating, fertility and pregnancy indices; and kidney tubule dilation – have all been forgotten, despite the fact that EPA toxicologists identified them as caused by glyphosate exposure after careful analysis of the studies submitted by registrants.

Several peer-reviewed animal studies on glyphosate and glyphosate formulations support its association with adverse effects on the liver and kidney, including metabolomic and proteomic markers of non-alcoholic fatty liver disease (Mesnage et al. 2015, Mesnage et al. 2017, Milic et al. 2018, Ren et al. 2019). Another study found glyphosate excretion is significantly higher in patients with nonalcoholic steatohepatitis, and a significant dose-dependent increase of glyphosate exposure with increase in fibrosis stages (Mills et al. 2019). Several studies suggest these effects may be mediated by the effects of xenobiotics, including glyphosate, on the gut microbiome (Bonvallot et al. 2018, Caussy et al. 2018). EPA concedes it does not collect guideline toxicity studies on the effects of pesticides on the gut microbiome (EPA 4/23/18, p. 9), so effects of this sort go unexamined. More study of glyphosate's impact on the gut microbiome is needed (Mao et al. 2018).

The decisions to consign these studies to regulatory oblivion have nothing to do with toxicology; their sin was that they provided the basis for human safety thresholds that were too low to support the vastly increased glyphosate to come, driven by the introduction of glyphosate-resistant crops and desiccant use of glyphosate on many crops. Therefore, they had to go. We next discuss available estimates of glyphosate exposure and how they have changed over time, and compare them to the safety thresholds.

[42] It is not clear why EPA initially set the cRfD at 2.0 mg/kg bw/day; apparently it simply rounded up from 1.75, then thought better of this questionable sleight of hand a few years later.

B. Human dietary exposure to glyphosate and its AMPA metabolite

Based on available information, most dietary (food + water) exposure to glyphosate is likely from residues in food. In 1983, EPA estimated that the general population was exposed to a maximum of 0.0071 mg/kg bw/day of glyphosate in food (EPA 3/3/83, pp. 4-5).[43] Due to a host of new glyphosate tolerances issued in the following decade, that figure had risen nearly four-fold to 0.025 mg/kg bw/day by 1993 (EPA 1993b, p. 23). EPA's latest 2017 estimate, following a quarter-century of still more tolerance-setting and raising, is 0.089771 mg/kg bw/day, twelve-fold more than in 1983 (EPA 12/12/17, Table 5.5, p. 21).[44]

Infants and toddlers have higher exposures than adults, due to greater consumption of food and water per unit body weight, among other factors. The subgroups with the highest maximum exposures in 1993 and 2017, respectively, were non-nursing infants less than 1 year old (0.058 mg/kg bw/day) and 1-2 year olds (0.228379 mg/kg bw/day) (EPA 1993b, p. 23; EPA 12/12/17, Table 5.5., p. 21). This represents a roughly four-fold increase in maximum exposure since 1993 for infants and toddlers.

These exposure estimates are substantially greater than the safety thresholds in force from the 1970s through 1992. The maximum exposure of the general population to glyphosate in 2017 is nearly twice the 0.05 mg/kg bw/day threshold, while that of toddlers is more than four-fold higher. The big 20-fold jump in the level of "safe" exposure to glyphosate discussed in the last section occurred just a few years before Monsanto introduced its first glyphosate-resistant crop, Roundup Ready soybeans, in 1996, followed in short order by glyphosate-resistant versions of cotton, canola and corn. Introduction of these Roundup Ready crops required tolerance increases for glyphosate residues on each of them, as did the introductions of Roundup Ready sugar beets and alfalfa, which came later. The other major factor driving increased glyphosate tolerances and exposure is expanding preharvest/desiccant use of glyphosate on cereal crops like wheat and oats, and a host of others.

These maximum exposure estimates are based on "unrefined" assessments, which are intended to be conservative, since they assume tolerance-level residues on all food commodities, and the assumption that glyphosate is used on 100% of the acreage of the respective crops (see e.g. EPA 12/12/17, p. 21). A "refined" assessment utilizing different assumptions regarding residue levels and acres treated with glyphosate would yield lower exposure estimates.

[43] We have subtracted EPA's estimate of exposure to glyphosate in "potable water," which comprises 70% of the total (food+water) exposure estimate, and is likely to be excessively conservative. EPA estimated far less glyphosate in drinking water in subsequent years, including the 2017 estimate discussed in the text.

[44] This latest estimate includes estimated exposure in drinking water, which however comprises only about 0.002 mg/kg bw/day, or a bit more than 2% of the total.

However, several factors need to be considered regarding the "conservatism" of EPA's maximum exposure estimates. First, glyphosate tolerances (maximum permitted residue levels) are established on the basis of residue field trials conducted by registrants, chiefly Monsanto, in which they spray the pertinent crop, measure residues, and report the results to EPA. Clearly, independent government testing is needed to verify that financially interested pesticide companies are not biasing their test results downward, or otherwise underestimating the amount of their products in the food supply.

Unfortunately, there has been shockingly little in the way of U.S. government testing for glyphosate residues in any food crops. Given the massive scale of glyphosate use, one would expect it to be among the many pesticides regularly tested for by the the USDA and FDA in their long-standing residue testing programs. Since 1991, however, the USDA's Pesticide Data Program has tested for glyphosate in only one year, 2010 (reported in 2011), when only a relatively small sample (300) of soybeans were tested (Gillam 4/20/15). The U.S. Government Accountability Office took USDA and FDA to task for their failure to test foods for glyphosate, among other pesticide residues (GAO 2014). Plans set in place in 2015 for USDA to begin testing foods for glyphosate were somehow derailed and never realized two years later (Gillam 3/23/17). By 2018, initial testing by FDA of granola, crackers, corn meal and corn for glyphosate residues found substantial presence in all samples, with tolerance exceeded for corn (Gillam 2018).

Second, glyphosate in plants and animals is broken down to some extent into the metabolite aminomethyl phosphinic acid (AMPA). Yet EPA excludes AMPA from the glyphosate tolerance expression, and does not account for AMPA residues when calculating dietary exposure to glyphosate. This decision was made in 1994, when EPA determined that "based on toxicological considerations, AMPA need not be regulated ***regardless of levels observed in foods or feeds,***" with a similar determination being made later for N-acetyl AMPA, a metabolite of glyphosate that is produced in DuPont glyphosate-resistant crops (EPA 12/12/17, p. 19, emphasis added). "Regardless of levels" suggests that EPA considers AMPA to be harmless at any exposure level, which is simply not the case. FDA scientists find AMPA to be "a toxicologically significant compound" (Chamkasem and Harmon 2016). EPA itself has limited toxicology data from short-term animal testing on AMPA that show it to be similar in toxicity to glyphosate (EPA 12/12/17, Table B.3, p. 30). Canada, the European Union and Australia all regard AMPA as similar in toxicity to glyphosate, which is why their maximum residue limits, or MRLs (equivalent to EPA tolerances) are based on the ***combined*** level of glyphosate and AMPA; their risk assessments also encompass dietary exposure to both compounds (for Canada, see EPA 12/17/17, p. 36, Table C.2; EFSA 2018; APVMA 2012).[45]

[45] The European Food Safety Authority is considering an option in which AMPA would be counted for tolerance enforcement of residues on crops with glyphosate-resistant varieties on the

While *Codex Alimentarius* includes only glyphosate in the residue definition, the authority it relies upon for setting its standards states that "glyphosate together with AMPA should be regarded as the residues of toxicological concern," and provides a stoichiometric formula for factoring AMPA residues into dietary risk assessments of glyphosate (JMPR 2005, p. 125). In short, EPA is alone among developed country regulators in entirely disregarding exposure to AMPA in the food supply.

AMPA is detected at significant levels in some crops. For instance, canola has been genetically engineered to express an enzyme (glyphosate oxidoreductase) that degrades glyphosate into AMPA, as well as a glyphosate-insensitive EPSPS enzyme. As would be expected, AMPA is detected at appreciable levels in tissues of this canola (Correa et al. 2016). Monsanto informed EPA long ago that "AMPA ranges up to twice the level of glyphosate" in glyphosate-resistant soybeans (EPA 3/2/94). Tests conducted by USDA's AMS in 2010 found glyphosate in 90% and AMPA in 96% of 300 soybean samples, with an average ratio of 1.25 parts AMPA to one part glyphosate. Combined levels of glyphosate and AMPA reached 38.5 ppm in one sample, nearly double the soybean glyphosate tolerance.[46] A USDA scientist who tested glyphosate-resistant soybeans found mean levels of 3.08 and 25.00 ppm glyphosate and AMPA, respectively, when glyphosate was sprayed during soybean bloom (Duke et al. 2003). Bohn et al. (2014) found mean levels of 3.3 and 5.7 ppm of glyphosate and AMPA in glyphosate-resistant soybeans, respectively. By excluding AMPA from the tolerance expression and in dietary risk assessments, EPA substantially underestimates combined exposure to both compounds, which are regarded by regulatory authorities worldwide as similar in toxicity. The true reason EPA excluded AMPA from the glyphosate tolerance expression and in dietary exposure assessments in 1994 had nothing to do with "toxicological considerations;" it was to facilitate introduction of Roundup Ready soybeans, which convert a substantial portion of the glyphosate sprayed on them into AMPA.

EPA's only assessments of dietary exposure to glyphosate, while intended to be conservative, are based almost entirely on registrant residue data that are largely unverified by government testing, and exclude a metabolite of equivalent toxicity. These estimates exceed safety thresholds that prevailed from the 1970s until 1992, but which were then dismissed in favor of one 20-fold higher, which facilitated introduction of Roundup Ready crops and expanded desiccant use of glyphosate.

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market, but not for other plant commodities; however, risk assessments would still include consideration of AMPA for all crops (EFSA 2018, p. 4).

[46] Based on analysis of data downloaded from USDA's Pesticide Data Program on 5/2/19. At https://www.ams.usda.gov/datasets/pdp, select PDP Database Search. Search terms: All Commodities, Glyphosate and AMPA, All Years. These data do not provide a statistically representative picture of glyphosate or AMPA residues in soybeans, particularly since all samples came from a single state, Missouri, in a single year.

C. Dermal absorption of glyphosate

Systemic exposure to glyphosate occurs not only via the diet, but also through the skin. The extent to which glyphosate is absorbed is important for all users. As EPA explains for pesticides generally: "Dermal absorption is a significant factor in occupational or residential exposure risk assessments since these exposures occur most frequently via the dermal route" (EPA 1998a, p. 14). Thus, it is incredible to learn that EPA does not have a single study in its database that assesses dermal absorption of glyphosate (EPA 12/12/17, p. 12). EPA justifies its failure to require registrants to submit such a study by noting the absence of "dermal hazard" (Ibid.) This is illegitimate on two counts. First, some glyphosate formulations clearly do present "dermal hazards" to users, as evidenced by the fact that injuries to skin that include "blisters, rash, pruritis, skin irritation, hives, welts, sores, burning skin, and peeling skin" are among the most frequent category (30%) of glyphosate adverse effect incidents reported to the Agency (EPA 6/3/09, pp. 12-14). While glyphosate alone may have low dermal toxicity, exposure to formulations containing glyphosate and surfactants can cause "severe dermal effects" (EPA 2/6/14, p. 8 ff.). Second, dermal injury is a "portal-of-entry" effect that is independent of systemic toxicity ensuing from absorption of glyphosate into the bloodstream (EPA 2002, pp. 3-28 to 3-29).

Surfactants increase dermal absorption of glyphosate in multiple ways. As explained by Monsanto, they remove lipids from the surface of the skin; spread out droplets of glyphosate solution on skin, increasing the area of skin contact; and decrease evaporation of water from the glyphosate solution, increasing the time of skin contact. The skin irritation effect of surfactants also increases blood flow in blood vessels just below the epidermis, increasing absorption of glyphosate in this way as well (Monsanto 2001). Different glyphosate formulations enhance dermal uptake of glyphosate differently, due to numerous compositional differences. "Ideally, all of the different glyphosate formulations would have to be tested for dermal uptake" (Ibid.).

Tests commissioned by Monsanto in 2001 to meet data requirements of European regulators illustrate the wide range of dermal absorption that occurs with different formulations. In tests of just two formulations (each at two different concentrations) using an animal model, dermal absorption of glyphosate ranged from 1.3% to 10.3% of the applied dose (TNO 2002). EPA reports 555 glyphosate products registered in the U.S. Monsanto's 2010 patent discusses hundreds of different surfactants and thousands of possible surfactant combinations in glyphosate formulations. Thus, it would be surprising if dermal absorption of glyphosate were not even greater than 10% in some of them. According to Monsanto: "Ideally, all of the different glyphosate formulations would have to be tested for dermal uptake" (Monsanto 2001). EPA apparently has no such data for even one.

Dermal absorption of glyphosate is a particularly important consideration in assessing the overall or aggregate systemic exposure to glyphosate in occupational and residential users of glyphosate formulations; and for toddlers playing on turf that has recently been sprayed with the herbicide. EPA's failure to require ***any*** dermal absorption data for ***any*** glyphosate formulation makes it impossible for the Agency to conduct an accurate assessment of aggregate systemic exposure to glyphosate, as required by the Food Quality Protection Act.

D. Inhalational exposure to glyphosate

Inhalation is a potentially important exposure pathway for glyphosate and AMPA, particularly given glyphosate's high-volume use in agriculture and other settings. While glyphosate has low volatility, it has ranked among the three top pesticides in spray drift episodes in the U.S. over a six-year period (AAPCO 1999, 2005), suggesting frequent exposure of famers, farmworkers and bystanders to glyphosate drift.

Glyphosate and its AMPA metabolite were detected in over 60% of air samples taken in Iowa and Mississippi in 2007 and 2008 (Chang et al. 2011), and comprised 65% of bulk pesticide deposition in Winnipeg, Canada in 2010 and 2011 (Farenhorst et al. 2015). A one-week study of silvicultural workers spraying glyphosate revealed that the workers' breathing zone contained glyphosate levels in air orders of magnitude higher than found elsewhere in ambient air (Jauhiainen et al. 1991). Studies in Argentina have revealed a high potential for inhalation of glyphosate and AMPA adhering to wind-blown particles of soil (Primost et al. 2017, Aparacio et al. 2018, Aparacio et al. 2013, Bento et al. 2017).

Upper respiratory complaints from inhalational exposue to glyphosate formulations have been frequently reported to EPA, to other agencies, and in the medical literature (EPA 6/3/09, p. 32 ff., EPA 2/6/14, pp. 7-8, 28-29). Epidemiology studies of farmers have found associations between glyphosate use and adverse effects likely related to inhalational exposure, including asthma and conditions predisposing to asthma (Hoppin et al. 2008, 2016; Slager et al. 2009, 2010; Guerra et al. 2002, Moscato et al. 2009). Rodent studies suggest a mechanism by which glyphosate induces inflammation of the airways, potentially explaining the associations between glyphosate exposure and the adverse effects identified in these epidemiology studies (Kumar et al. 2014).

EPA concluded that inhalation of glyphosate has no toxic effects based on a rat study submitted to the Agency by Monsanto in 1983 (EPA 12/12/17, pp. 8; Table B.3, 30). This 28-day inhalation toxicity study was used to fulfill the requirement for a 90-day study (Ibid., Table B.1, p. 29), but is in any case "not capable of determining those effects that have a long latency period for development (e.g. carcinogenicity and life shortening)…" (EPA 1998b). Effects not captured by this study would also include asthma and many related respiratory conditions.

EPA has also failed to assess the contribution of inhalation to overall systemic exposure to glyphosate. This is based on the same false rationale given for EPA's failure to assess dermal absorption: lack of local (here, inhalational) effects in a short-term rat study.

E. Aggregate exposure to glyphosate

EPA cannot assess the level or effects of aggregate exposure to glyphosate and its metabolites without adequate data on systemic absorption of the herbicide and its breakdown products by all relevant routes of exposure: dietary as well as dermal and inhalational. Thus, the Agency's assessments of risk to occupational and residential users, and in other related scenarios, are deficient.

IX. Glyphosate Formulations and Human Health

The great majority of data collected for assessment of glyphosate's human health impacts is from tests done on glyphosate technical, the active ingredient sans surfactants or other formulation components. This includes all of the animal trials discussed above under the chronic toxicity section.

As observed by EPA's Health Effects Division, the human health impacts of glyphosate tend to differ by formulation, depending on the particular salt form of glyphosate and the identity and level of surfactants such as POEA (EPA 2/6/14, p. 7). As noted above: "There is insufficient evidence to conclude that glyphosate preparations containing POEA are more toxic than those containing alternative surfactants" (Bradberry et al. 2004).

EPA makes no attempt to utilize its own information on glyphosate formulation composition to help clarify this important issue, but instead references a report by a contractor to USDA's Forest Service (Durkin 2011) that according to EPA's summary of it provides next to no information on the surfactant composition of various glyphosate formulations (EPA 2/6/14, Appendix A, pp. 52-53).

A. Assessment and regulation of POEA and similar surfactants: Europe vs. the EPA

Available data on the toxicity of surfactants is limited largely to POEAs. In 2015, the European Food Safety Authority evaluated a summary of the available toxicological information on POEAs compiled by German regulators (EFSA 2015). While EFSA found that information inadequate to perform a full risk assessment, it observed that the few available animal studies indicated that POEAs exhibited acute oral, dermal and ocular toxicity; genotoxicity; and reproductive impacts on males and females that triggered the need for investigations into their

endocrine-disruption potential. EFSA also found that: "There is no information regarding the residues [of POEAs] in plants and livestock." Overall, the available data were insufficient to establish safety thresholds for acute or chronic exposure for the general population, or for applicators. More data were needed on the genotoxicity, long-term toxicity, carcinogenicity, reproductive and developmental toxicity and endocrine-disrupting potential of POEAs. In consequence of this review, member states backed a proposal by the European Commission to ban the use of POEA in all glyphosate-based herbicides, including Roundup (Michalopoulos 2016), and the European Commission enacted this ban soon thereafter (EU 2016).

In 2009, EPA renewed a pre-existing exemption from the requirement of a tolerance for a broad class of surfactants known as alkyl amine polyalkoxylates (EPA 6/17/09). This class (henceforth AAPs) includes POEAs and related compounds that are known to be used in glyphosate formulations. The human health assessment associated with this tolerance action (see EPA 4/3/09 for the following) was based on a petition from a consortium of industry groups, which included information and limited animal test results on just four compounds from this broad class. EPA established a chronic oral NOAEL of 15 mg/kg bw/day based on a subchronic (90-day) study in rats, and a corresponding chronic reference dose (cRfD) of 0.15 mg/kg bw/day (EPA 4/3/09, Table 4.5, pp. 16-17). This chronic oral endpoint also covers incidental short-term and intermediate term oral exposures, and serves as the reference dose for dermal and inhalational exposure for all durations (Ibid.).

POEA (aka MON 0818) and/or several other known members of this AAP class are classified in Toxicity Category II (severely irritating to corrosive) in the primary skin irritation study in rabbits; in Toxicity Category I (causes tissue destruction) for primary eye irritation in rabbits; and as dermal sensitizers in the dermal sensitization test in guinea pigs (EPA 4/3/09, Table A.1, pp. 53-54). In its 1993 reregistration decision for glyphosate, EPA confirms that some glyphosate formulations likewise fall into Toxicity Categories I and II for injury to eye and skin (EPA 1993b, p. 22), likely due to the presence of these or related surfactants.

EPA found substantial risks of concern to occupational users of pesticides containing AAPs, but dismissed them on the grounds that its assessment was conservative, despite having animal data on just 4 AAP compounds, and lacking critical data in numerous areas. Data gaps include lack of studies on chronic toxicity and carcinogenicity, as well as lack of information on dermal absorption, metabolism and endocrine disruption potential. The lack of metabolism data was justified by reference to studies on another class of surfactants. Dermal absorption was guesstimated based on modeling of structurally similar surfactants. Carcinogenicity was ruled out based on a structure activity relationship database (DEREK11) that did not produce any "structural alerts for a representative large molecule…" Endocrine disruption was flagged as a potential concern, but was not tested because EPA did not have protocols in place.

While the European Union banned POEA surfactants from glyphosate formulations, EPA renewed its approval of POEAs and similar AAP surfactants at up to 25% by weight in herbicide formulations, and with no limit established for AAP residues in or on food crops, and without requiring protections for applicators.

It is interesting to note that EPA's oral, dermal and inhalational reference doses for AAPs are nearly 7-fold lower than its proposed cRfD for glyphosate of 1 mg/kg bw/day.

X. Glyphosate, Glyphosate Formulations and Cancer

CFS incorporates by reference our discussion of glyphosate's carcinogenic hazard in our 2018 comments. Additonal information and analysis is presented below.

A. EPA biases assessment to dismiss evidence of carcinogenicity

EPA continues to maintain that it followed its 2005 Guidelines for Carcinogen Risk Assessment in evaluating glyphosate (EPA 2019, p. 7), which is manifestly untrue. CFS demonstrated that EPA consistently and blatantly violated basic rules for interpretation of evidence from carcinogenicity animal feeding trials that are established in those Guidelines, and which are common to the OECD's and other organization's carcinogenicity risk assessment protocols (CFS 2016a). EPA also distorted the meaning of "limit dose," which is clearly defined in its carcinogenicity testing protocols, as meaning a dosage level beyond which tumors can be discounted, when in fact the term designates the dosage level that need not (but can) be exceeded, if it is not a maximally tolerated dose (Ibid.) The Scientific Advisory Panel that reviewed EPA's evaluation of glyphoate's carcinogenic hazard also found that EPA defied its Guidelines in several critical respects (following references to SAP 2017):

1) EPA's discounting of statistically significant trends that did not increase monotonically was not supported by the Guidelines (p. 50);
2) EPA's biased use of historical control tumor incidence data to discount, but never support, the biological significance of statistically significant findings (pp. 60-63);
3) Improper dismissal of tumor data in groups exceeding the supposed "limit dose" of 1,000 mg/kg/day, whereas the Guideline limit is either the maximally tolerated dose, or 5% of the test substance in feed (pp. 72-74);
4) An excessively stringent four-part rule demanding statistically significant pairwise comparisons AND trends, AND monotonic trend AND a concurrent control incidence that closely resembles historical control incidence (p. 51); and
5) EPA's attempt to turn the hazard evaluation into a risk assessment (pp. 20, 80).

EPA's assessment of glyphosate's carcinogenic potential is also entirely at odds with its past practice. In supplemental comments to SAP (2017), CFS compared EPA's carcinogenicity assessment of glyphosate to those of two other pesticides that EPA classified as likely to be

carcinogenic to humans (the herbicide isoxaflutole and the fungicide iprovalicarb), and found the latter two assessments adhered much more closely to EPA's Guidelines than did its glyphosate assessment (see CFS 2016b and references therein for the following discussion).

With respect to dosing, EPA found both compounds to be likely carcinogenic based ***primarily*** on tumor incidences in groups receiving more than the "limit dose" of 1,000 mg/kg/bw, while those findings were discounted for glyphosate. Moreover, while EPA was concerned exclusively with potentially excessive dosing with glyphosate, the Agency showed equal concern that it be adequately high to ensure a sufficiently stringent test of carcinogenicity for the other two compounds.

There is no mention of "monotonic dose response" as a criterion of significance for tumors with the latter two compounds, while it played a substantial role in discounting statistically significant tumor incidence for glyphosate.

EPA found isoxaflutole to be likely carcinogenic based on two rodent studies with treatment-related tumor findings, and iprovalicarb to be likely carcinogenic based on one positive rat study and one negative mouse study. Properly interpreted, at least four of seven rat studies and five of five mouse studies provide evidence of glyphosate's carcinogenicity (CFS 2016a).

EPA's evaluation of glyphosate's carcinogenic potential not only violates its relevant Guidelines in numerous respects, it is also at odds with the Guideline-compliant approach the Agency applied in assessing the carcinogenicity of two other pesticides that are likely human carcinogens: isoxaflutole and iprovalicarb.

B. <u>Dermal and inhalational exposure</u>

As noted in the recent report on glyphosate toxicology by the Agency for Toxic Substances and Disease Registry, an agency of the U.S. Department of Health and Human Services: "Dermal contact appears to be the major route of exposure to glyphosate for people involved in its application," and farmers and residential users are also exposed to glyphosate vis "inhalation of mist or spray during use of the products containing this chemical" (ATSDR 2019, p. 2).

EPA's assessment focuses heavily on dietary exposure to glyphosate, and takes insufficient account of systemic exposure to the herbicide via the dermal and inhalational routes. Those who load, mix and/or apply glyphosate formulations will inevitably get some on their skin. As discussed above, dermal absorption of glyphosate is enhanced by formulation additives, and varies considerably by formulation. Inhalation of glyphosate spray and/or glyphosate

adsorbed to windblown particles of soil will also be a frequent occurrence. Absorption of glyphosate into the bloodstream via the dermal and inhalation routes in these situations could contribute substantially to systemic toxicity, and may well help explain the increased incidence of non-Hodgkin lymphoma (NHL) observed in epidemiology studies of farmers and pesticide applicators. It is also worth noting that many of the cancer lawsuits against Monsanto have been brought by people who have contracted NHL after many years of regular use of Roundup herbicides in residential or occupational settings.

C. Glyphosate persists in bone and bone marrow

EPA's cancer assessment of glyphosate included a brief discussion of glyphosate's absorption, distribution, metabolism and excretion (ADME), data that "may provide valuable insights into the likelihood of human cancer risk from exposure" to glyphosate (EPA 12/12/17, p. 93). ADME studies are conducted in experimental animals to assess a xenobiotic's distribution within the body, its potential metabolism into breakdown products, and the rates at which it is absorbed into the bloodstream and excreted. EPA's conclusions from the mostly uncited studies it reviews were that "the amounts of glyphosate detected in tissues were negligible indicating low tissue retention following dosing," that most glyphosate was excreted unchanged in feces and urine, and that "elimination was essentially complete by 24 hours indicating that glyphosate does not bioaccumulate."

The cancer most associated with glyphosate exposure in human epidemiology studies is non-Hodgkin lymphoma (NHL), a cancer that begins in lymphocytes, which are infection-fighting white blood cells produced by lymph tissue. NHL can originate anywhere lymph tissue is found – including lymph nodes, spleen, thymus and bone marrow – and spread to other parts of the lymph system (ACS undated). Thus, it might be of interest to learn whether glyphosate is distributed to organs with lymphatic tissue, where it could potentially affect the development of lymphocytes. Below, we discuss several ADME studies in which radiolabeled glyphosate was measured in various tissues, such as bone and bone marrow, of experimental animals dosed with the herbicide.

Monsanto scientists Brewster et al. (1991) found 4.7% of the glyphosate they fed to rats was in their bones 6.3 hours later, with 1.1% still present after seven days. Elimination followed a two-phase pattern, with a very short period of rapid elimination followed by a second phase in which glyphosate levels in bone declined much more slowly. Glyphosate levels were not reported in bone marrow specifically.

Several other studies arrived at more or less similar results (see JMPR 2004, pp. 96-103 for the following discussion and references). Ridley (1983) measured glyphosate in blood plasma and bone marrow of rats at several timepoints up to 10 hours after an intraperitoneal

injection, and found rapid elimination of glyphosate from plasma, but slower elimination from bone marrow (JMPR 2004, pp. 96-97).

Powles (1992a) administered glyphosate orally to rats and measured its presence in various tissues 4, 10 and 24 hours later. At both 10 and 24 hours, bone and bone marrow were among the tissues with the highest levels of glyphosate (JMPR 2004, p. 99). Powles (1992b) had similar results in experiments involving oral administration of single or repeated doses, and intravenous admintration, of glyphosate to different groups of rats. After 7 days, "[t]he highest concentration of glyphosate was found in bone, with lower concentrations in bone marrow, kidney, liver, lungs and the residual carcass" (JMPR 2004, pp. 99-101, Table 7).

Davies (1996a, 1996b, 1996c) conducted similar studies, only the rats were sacrificed and tissues measured for glyphosate after only 72 hours. These studies also found by far the highest levels of glyphosate remaining in the rats were in bone tissue, whether the glyphosate was administered orally in one or repeated doses. Bone marrow was apparently not tested separately from bone (JMPR 2004, pp. 100-102).

While most glyphosate administrered to test animals is rapidly eliminated via feces and urine, multiple studies show that a significant amount is retained in bone tissue, including bone marrow, even 7 days after administration (none of the studies discussed above went beyond 7 days). The mineral portion of bone is composed of hydroxyapatite (aka hydroxylapatite). The calcium is present as a divalent cation (ion with 2 positive charges). Glyphosate is known to chelate (bind to) divalent cations, including Ca^{2+}, for instance in plant tissues (Cakmak et al. 2009). This represents a possible mechanism for glyphosate's relative persistence in bone tissue.

There is strong evidence that glyphosate and its formulations have genotoxicity both *in vivo* and *in vitro* (IARC 2015, Benbrook 2019). This evidence includes a number of positive results for glyphosate's genotoxicity in bone marrow and lymphocytes. Bolognesi et al (2009) found increased micronucleus formation in the peripheral blood lymphocytes of people living in areas of Columbia with aerial spraying of glyphosate formulations, with increases also observed in individuals tested after spraying operations took place vs. baseline levels measured prior to spraying (Bolognesi et al. 2009). Glyphosate and its formulations have proven to be genotoxic to human lymphocytes in a number of *in vitro* tests as well (IARC 2015, Table 4.2, pp. 49-50). *In vivo* tests in non-human mammals have demonstrated that glyphosate induces micronucleus formation or chromosomal aberrations in bone marrow (IARC 2015, Table 4.3, pp. 52-53), while *in vitro* genotoxicity assays in non-human mammalian cell cultures have also shown that glyphosate, its formulations, and AMPA can cause chromosomal damage (IARC 2015, Table 4.4, p. 55).

D. Glyphosate contaminants

EPA refers to analyses showing that over 92% of technical glyphosate samples that were tested contained less than 1.0 ppm N-nitrosoglyphosate, a potentially carcinogenic contaminant, and that EPA policy is to require carcinogenicity testing of pesticides contaminated with N-nitroso contaminants at levels greater than or equal to 1.0 ppm (EPA 4/23/18, p. 8).[47] EPA's 1980 policy notes that 80% of the 80 N-nitrosamines that had been tested for carcinogenicity at that time had been found to be carcinogenic in a variety of species. It is not clear why the presence of a potential carcinogen at levels of concern to EPA in over 7% of batches of technical glyphosate is regarded as "not toxicologically significant" (Ibid.). We see no evidence that EPA has ever collected valid data on the potential carcinogenicity of N-nitroso-glyphosate or other N-nitroso contaminants in glyphosate or its formulations.

E. Glyphosate formulations and cancer

The animal trials and NNG contamination discussed above relate to glyphosate technical, leaving the effects of exposure to glyphosate formulations largely unexamined. As Monsanto toxicologist Donna Farmer put it in an email to colleagues: "The terms glyphosate and Roundup cannot be used interchangeably nor can you use 'Roundup' for all glyphosate-based herbicides any more. For example you cannot say that Roundup is not a carcinogen…we have not done the necessary testing on the formulation to make that statement. The testing on the formulations are not anywhere near the level of the active ingredient" (Farmer 2003).

One concern is the toxicity of POEA and similar surfactants. While as discussed above the EU banned POEAs for use in glyphosate formulations due to evidence of a number of serious harms, and lack of animal trials assessing carcinogenicity and other endpoints, EPA permitted continued heavy use (at up to 25% by weight in herbicide formulations).

As noted above, both glyphosate and glyphosate formulations have tested positive for genotoxicity in numerous assays (IARC 2015). Benbrook (2019) conducted an updated analysis of the genotoxicity data, finding that assays by independent scientists are much more likely to give positive results than those by pesticide registrants in unpublished studies submitted to EPA, among other findings. In addition, the U.S. National Toxicology Program is conducting *in vitro* studies that compare the ability of glyphosate versus its formulations to induce oxidative stress (another mechanism of carcinogenicity), which may provide useful information in the future.

Glyphosate epidemiology studies arguably provide the most relevant evidence, because by their very nature, they assess the outcome of real-world exposure to glyphosate formulations.

[47] For the policy, see: "Pesticides Contaminated with N-nitroso Compounds," Federal Register, Vol. 45, No. 124, 42854-858, June 25, 1980.

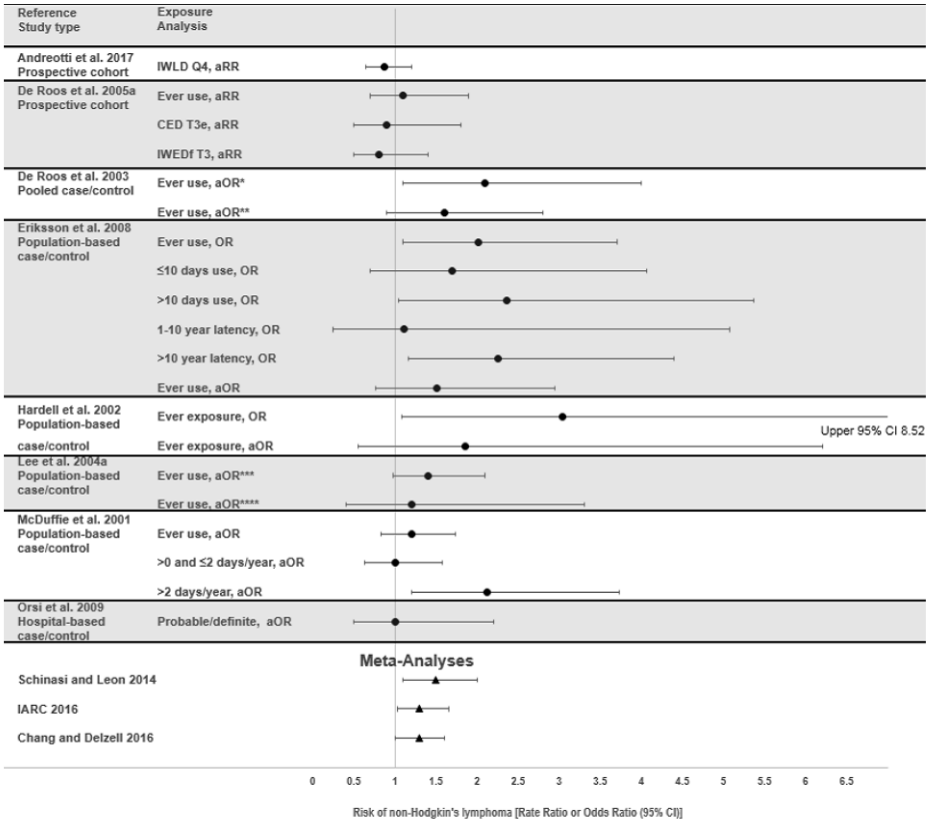
Therefore, it is odd that EPA seems to regret not having epidemiology studies on glyphosate alone, which is not used in the real world, and regards formulation data as somehow second-best: "The epidemiological data was considered in this evaluation since it represents the best available data for evaluating human exposures and potential risk of cancer in the absence of epidemiological data on the active ingredient alone" (EPA 4/23/18, p. 2).

IARC (2015) found credible but not definitive evidence that glyphosate formulations cause non-Hodgkin lymphoma, based on three epidemiology studies showing increased odds of NHL among glyphosate-using applicators, and others that did not find this association. EPA focused heavily for its contrary view on the Agricultural Health Study (De Roos et al. 2005; updated in Andreotti et al. 2018), which did not find an association between glyphosate use and NHL incidence in U.S. applicators.

When individual studies give conflicting results, meta-analyses that evaluate the results of multiple studies can be useful. An advantage of meta-analyses is that their outcomes are based on much larger numbers of exposed individuals and cancer cases than individual studies, reducing the effects of random variation. Three metaanalyses – Schinasi and Leon (2014), Chang and Delzell (2016), and IARC (2017) – found increased relative risks of NHL among glyphosate-using applicators of 1.5, 1.3 and 1.3, with the lowerbound 95% confidence interval in each case $\geq$ 1.0 and the upperbound confidence interval ranging from 1.6 to 2.0 (ATSDR 2019, Table 2-6, pp. 54-55; see also graphic below). A more recent meta-analysis by Leon et al. (2019) that encompassed 316,270 farmers or agricultural workers from France, Norway and the U.S., and 2,430 cases of NHL, found a meta-hazard ratio of 1.36 (95% confidence interval from 1.00-1.85) for diffuse large B-cell lymphoma, a major NHL subtype, and glyphosate use.

A fifth meta-analysis took a somewhat different approach. Zhang et al (2019) hypothesized that if an association between glyphosate exposure and NHL exists, it should be most pronounced in those most highly exposed to glyphosate. Their metaanalysis encompassed six studies, including the updated Agricultural Health Study (Andreotti et al. 2018), and found that more highly exposed glyphosate users had a 41% elevated risk of contracting NHL: meta-relative risk = 1.41, 95% confidence interval: 1.13-1.75.

Figure 2-4. Risk of non-Hodgkin's Lymphoma Relative to Self-Reported Glyphosate Use or Exposure



*Logistic Regression; **Hierarchical regression; ***Non-Asthmatic farmers; ****Asthmatic farmers

a = adjusted; CED = cumulative exposure; IWED = intensity-weighted exposure days; IWLD = intensity-weighted lifetime days; OR = odds ratio; Q4 = 4th quartile; RR = rate ratio; T3 = 3rd tertile

Source: ATSDR (2019), p. 86. The point estimates, which best represent the study results, are represented by filled circles or triangles in the graph above; point estimates to the right of the vertical line indicate increased risk of NHL, those to the left lesser risk. The lines indicate the 95% confidence interval.

In short, there is now very strong epidemiological evidence of an association between glyphosate exposure and NHL, as illustrated by the graph above, reproduced from the draft report on glyphosate's toxicology by the U.S. Agency for Toxic Substances and Disease Registry. (This figure excludes the two very recent metaanalyses discussed above, Leon et al. (2019) and Zhang et al. (2019), which both considerably strengthen the association.)

EPA's continuing denial of an association between glyphosate exposure and NHL is based in part on rejection of studies with 95% confidence intervals whose lower bound encompasses 1.0 – an excessively stringent criterion of statistical significance that has recently been criticized as illegitimate in a *Nature* article with over 800 signatories (Amrhein et al. 2019). The authors remind readers that "not all values inside [the 95% confidence interval] are equally compatible with the data … The point estimate is the most compatible, and values near it are

more compatible than those near the limits." They add: "It is ludicrous to conclude that statistically non-significant results showed 'no association', when the interval estimated included serious risk increases."

In 2015, EPA's science division – the Office of Research and Development (ORD) – reviewed a draft of the Office of Pesticide Program's (OPP's) glyphosate cancer assessment, and discussed in particular the proper classification of glyphosate into one of five categories of carcinogenic hazard, as defined in EPA's 2005 Guidelines. ORD's epidemiologists agreed with IARC on the epidemiological evidence for glyphosate, and noted that this alone would rule out "not likely to be carcinogenic," the classification OPP eventually chose. ORD presented their "nuanced evaluation of the epidemiology" to OPP, but "OPP insisted on dichotomizing this to be either 'causal' or 'not 'causal'," in violation of its cancer assessment Guidelines (EPA 12/7/15). ORD noted OPP's deviations from the Guidelines in its interpretation of animal studies as well, and described the criteria for the different carcinogenic hazard categories (EPA 12/14/15). ORD's Vincent Cogliano described the views of ORD scientists who had reviewed the glyphosate materials, concluding that they would be split between classifying glyphosate as "likely to be carcinogenic" and as "suggestive of carcinogenicity" (EPA 12/7/15).

F. Lack of carcinogenicity testing of glyphosate metabolites

EPA has not, as it claims, assessed the glyphosate metabolites AMPA or N-acetyl glyphosate for cancer effects (EPA 2019, p. 19). EPA lists two 90-day animal feeding studies and one prenatal developmental study for AMPA, but no study assessing carcinogenicity (EPA 2019, Table B.3, p. 30). There is also no animal carcinogenicity feeding trial for N-acetyl glyphosate, but rather only a few genotoxicity tests and a "lack of structural alerts for carcinogenicity" based presumably on *in silica* comparisons of its structure to the structures of carcinogens we happen to have some knowledge of (Ibid., pp. 19; Table B.4, pp. 33-34). The exhaustive bibliography of registrant studies on glyphosate supplied by EPA does not appear to contain any assessing the carcinogenic potential of AMPA (EPA Bibliography undated).

XI. Environmental Impacts of Glyphosate Use

A. Glyphosate Toxicity to Terrestrial Plants

As discussed more fully in our 2018 comments, EPA's choice of the cucumber as the most sensitive dicot species (IC_{25} = 0.074 lb. a.e./acre) in establishing the terrestrial plant toxicity threshold was mistaken. A host of other plants are more sensitive to glyphosate, as demonstrated in high-quality studies conducted by EPA scientists and others who used EPA-prescribed endpoints. These include Pfleeger et al. (2011): EC_{25} values for above-ground biomass of potato as low as 0.003 lb. a.i./acre; Olszyk et al. (2013), who exposed 17 prairie plant species to four concentrations of Roundup Original, an isopropylamine salt, and found IC_{25} values for the six

most sensitive species ranged from 23 to 54 g a.i./ha, which translates to 0.021 to 0.048 lb a.i./acre, or 0.015 to 0.034 lb. a.e./acre. Likewise, Boutin et al (2004) found EC_{50} values for 15 plant species exposed to Roundup Bio ranging from 0.009 to 0.053 lb. a.e./acre. All of these threshold are below that of the cucumber, as measured in a registrant study. Two of the studies summarized above were conducted by teams of EPA plant scientists (Olszyk et al 2013, Pfleeger et al 2011), who thoroughly understand EPA testing protocols. The third, Boutin et al. (2004) was also conducted according to EPA protocols. EPA can have no reasonable basis for rejecting these studies.

EPA states that common milkweed is of similar sensitivity to glyphosate as cucumber (EPA 11/21/18, p. 8). In fact, one of just two studies considered by EPA shows it is roughly twice as sensitive, with an IC_{25} alue of 0.04 lb. a.i/acre, as discussed in our 2018 comments.

Even with the cucumber toxicity threshold, EPA's preliminary ecological risk assessment concluded that the drift of glyphosate formulations to plants may impact the survival and/or reduce the biomass of upland plants and riparian/wetland plants adjacent to treated fields. Use of the proper, lower toxicity threshold discussed above would sharply increase the distance from the glyphosate-treated field at which harm above the IC_{25} threshold occurs.

B. Glyphosate and Monarch Butterflies

EPA states that conservation of monarchs is an important issue but downplays the role of pesticides in their decline with a litany of other possible stressors (EPA 2019, pp. 11-12). Specifically, as addressed in our 2018 comments to this docket, EPA still does not acknowledge the central role of glyphosate use in the decline of monarchs, in spite of abundant evidence. EPA then lists its general plans to manage risks to monarchs from pesticides, which are almost entirely voluntary actions, educational materials, and advisory label language on herbicides generally, basically saying please try your best to keep this pesticide from drifting (EPA 2019, pp. 12-14).

Yet EPA's proposed drift mitigations are inadequate to protect sensitive non-target organisms from glyphosate – more wishful thinking than evidence of efficacy. And EPA has shown in the PID that milkweed is very sensitive to glyphosate indeed, requiring substantial buffers from the edge of treated fields to protect it from a certain level of injury (EPA 2019, p. 29).

Buffer zones are clearly needed to protect both common milkweed and other sensitive plants in agricultural areas where glyphosate formulations are sprayed. Such buffer zones must be based on the most sensitive endpoints, as discussed above, and thus be considerably larger than those portrayed in Table 49 (EPA 9/8/15, p. 94).

EPA's proposed measures to "mitigate" spray drift damage to common milkweed and other terrestrial plants in agricultural areas would be entirely ineffective (EPA 2019, pp. 35-37). Given that field edges and roadsides provide substantial habitat for milkweeds and monarchs, it is especially important that EPA include serious mitigations based on rigorous scientific analyses and proven drift-reduction methods, such as mandatory spray buffers, reductions in application amounts, bans on aerial applications, and other appropriate restrictions where monarch habitat is at risk.

The prohibition against spraying during temperature inversions is infeasible, given the frequency of such conditions during the spring and summer spraying seasons in much of the country where glyphosate is used, for instance the Corn Belt (Bradley 2017), and the inability of applicators, who are after all not meteorologists, to reliably determine when temperature inversions occur. EPA presents no assessment or rationale for believing that the "temperature inversion" or the other "spray drift management" mitigations would have the slightest real-world effect in reducing glyphosate formulation spray drift frequency or distance.

The second drift-related "mitigation" is even less helpful: the proposal to add a "non-target organism advisory statement" to glyphosate formulation labels (EPA 2019, pp. 37-38). The statement would merely tell growers that they should follow "label directions intended to minimize spray drift" in order to "protect the forage and habitat" of unspecified "non-target organisms." It is hard to imagine a more ineffectual advisory statement. It assumes applicators understand which "non-target organisms" are put at risk by glyphosate formulations, and what their forage and habitat requirements are. Even assuming such understanding, the "advice" given that they should follow label directions is entirely redundant, since label directions are theoretically enforceable, although in practice rarely if ever enforced.

Another consideration is the large range of surfactants and surfactant combinations that are likely deployed in different glyphosate formulations, as reflected in Monsanto's patent, discussed above (Monsanto 2010). This patent reports on weed efficacy studies and gives other information on glyphosate formulations containing a dizzying array of surfactants and surfactant combinations. Monsanto lists 166 proprietary excipients (i.e. mostly surfactants, but also other "inerts") used in its testing (Ibid, par. 0407). Hundreds to thousands of these novel glyphosate formulations containing from 1 to 3 of these excipients are tested for efficacy against several weeds, with their performance compared to glyphosate alone (sans additives) and commercial glyphosate produts at various rates (Ibid., pars. 0416 to 0613). The wide range of efficacy of different tested formulations indicates that the plant-damaging effects of drift at a given distance will likewise vary considerably based on the specific formulation. Monsanto claims that some surfactants create or enlarge channels through the leaf cuticle to enhance uptake of glyphosate, and/or enhance translocation of glyphosate throughout the plant (Ibid., pars. 0211, 0214, 0238).

Significantly, "some of the mixtures are synergistic, in that they are mixtures of surfactants which, when tested individually, did not form anisotropic aggregates and/or epicuticular liquid crystals [i.e. mechanisms for enhancing glyphosate absorption]" (Ibid., pars. 239-240).

Hence, the distance drift can damage to injure off-target plants will vary by formulation, and results of testing with one or several "typical end use products" will not capture this variability. Drift from some formulations will inevitably be more damaging at a given distance off-field than the "typical" end use product that happens to be tested.

C. Glyphosate and Risks to Aquatic Organisms

In our 2018 comments, CFS discussed numerous peer-reviewed studies demonstrating the extreme toxicity of glyphosate formulations (with or without POEA) and POEA to aquatic organisms, particularly aquatic-phase amphibians. We also discussed flaws in EPA's assessment of aquatic organism exposure to glyphosate formulations and POEA in particular, which we summarize and supplement below.

EPA underestimates exposure of aquatic organisms to glyphosate and associated surfactants in several ways. First, EPA assumes surfactants in terrestrial formulations degrade rapidly in the soil and do not runoff into bodies of water. This is not the case. POEAs in particular persist for months in the soil and ARE available for runoff (Tush and Meyer 2016). In its response to comments, EPA concedes that POEA may persist and enter aquatic environments, but does not change its risk assessment accordingly (EPA 11/21/18, p. 3). Second, EPA assumes that terrestrial applications of glyphosate formulations never involve direct oversprays of aquatic habitats (but rather only drift from a nearby field). This is not the case. Direct oversprays are a common occurrence, as we documented. They certainly occur in forestry applications, and vernal pools in forests are important amphibian habitat. For glyphosate formulations labeled for both aquatic and terrestrial uses, EPA proposes to exempt aerial applications over the forest canopy from the general terrestrial use prohibiton against direct application to bodies of water (EPA 2019, p. 39). Third, EPA's modeling of glyphosate (and hence surfactant) concentrations in water from runoff and drift are based on relatively large bodies of water that will underestimate concentrations in smaller bodies, such as vernal pools, where concentrations of glyphosate up to 0.328 mg/liter have been recorded (Battaglin et al 2009).

An additional factor is that EPA's entire aquatic exposure assessment with respect to surfactants is limited to POEA, and is based on the assumption that glyphosate formulations contain only 15% POEA (EPA 9/8/15, p. 27). The source for 15% POEA is a report by USDA contractors,[48] and is contradicted elsewhere by EPA's own Health Effects Division, which

[48] The reference is to "Diamond and Durkin, 1997," which however is not listed in the bibliography for this document. CFS found the document (see References section). On page 14,

reports that POEA comprises or has comprised up to 50% of some glyphosate formulations (EPA 2/6/14, p. 6). Since 2009, POEA and POEA-type surfactants are permitted in herbicide formulations at concentrations up to 25% by weight (EPA 6/17/09). This 15% figure serves as the basis for EPA's entire assessment of POEA-containing formulation toxicity to aquatic organisms (EPA 9/8/15, pp. 27 ff, see e.g. Figure 5 and 6, p. 29). Thus, EPA's entire assessment substantially underestimates exposure of aquatic organisms to formulations with POEA-family surfactants that contain them at concentrations above 15%.

EPA likewise makes reference to an uncited "LUIS report" for data on glyphosate formulations, data whose inadequacy forces the Agency to make assumptions that introduce "uncertainty" into its calcuations (EPA 9/8/15, pp. 15, 27).

EPA must conduct a new assessment of glyphosate formulation toxicity to aquatic organisms that accounts for the various errors discussed above, both in terms of exposure levels (estimated environmental concentrations) and toxicity thresholds, which should be based on high-quality peer-reviewed literature on the most sensitive organisms.

D. Glyphosate and Risks to Pollinators

It is urgent that pesticides be evaluated for impacts on pollinators and other beneficial insects. Populations of many insect species are in decline (e.g. Wepprich et al. 2019, introduction at 1-2: "…a global analysis of long-term population trends across 452 species estimated that insect abundance had declined 45% over 40 years [1]. Recently, more extreme declines in insect biomass have been observed upon resampling after 2–4 decades [4,5]), and several pesticides including glyphosate are implicated (Wepprich et al. 2019, summary at 15-16).

However, EPA has not fully evaluated effects of glyphosate use on pollinators and other beneficial insects, but instead has put off this requirement and may ask for more studies (EPA 2019, pp. 14, 28).

EPA's evaluation of the effects of glyphosate use on pollinators and other beneficial insects must take into account the particular life histories and characteristics of different kinds of insects, not just honeybees. Given the great diversity of species, EPA must use the best available science, including studies done by independent researchers using a variety of toxicity endpoints: acute and chronic toxicity of glyphosate to the insects, sublethal impacts such as increased susceptibility to pathogens and parasites, changes in foraging behavior (Balbuena et al. 2015), and other aberrant changes (Faita et al. 2018) that are likely to result in lowered fitness. For

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the authors state: "The [POEA] surfactant in Roundup is present at 15% (Hoogheem 1987, Sawada et al. 1988), or 150 g/L assuming that the 15% value refers to the level in terms of weight per unit volume."

example, recent studies show that glyphosate is toxic to bee's gut microflora (Motta et al. 2018 a and b, Blot et al. 2019), which could have significant health effects.

Many of these insects depend on habitat near agricultural fields that is vulnerable to off-site movement of glyphosate in drift and run-off (Botías et al. 2019, Boutin et al. 2019). Glyphosate thus indirectly impacts pollinators and other beneficial insects via habitat degradation and destruction, including changes to species composition in affected environments since some plant species are more sensitive to glyphosate than others (Boutin et al. 2019, Cederlund 2017 a and b, Olszyk et al. 2017, Saunders and Pezeshki 2014, 2015; Saunders et al. 2013). Research shows that glyphosate use can result in changes in plant reproduction that affect which species are abundant or rare in later generations as well (Boutin et al. 2019, Olszyk et al. 2017), and thus what resources are available for particular insects.

E. Glyphosate Toxicity to Birds

Based on EPA's preliminary ecological assessment, glyphosate clearly poses chronic risks of concern in at least six glyphosate application scenarios (EPA 2019, pp. 26-27). This is true even though EPA does not have a valid NOAEC for harm to avian species. The lowest dose tested in the mallard reproduction study (501 mg ae/kg) was found to have adverse effects; both the LOAEC and the NOAEC are less than 501 mg ae/kg. Risk quotients exceeded the agency's level of concern in six glyphosate application scenarios even with illegitimate use of the non-definitive NOAEC from the less sensitive study in bobwhite quail. These risk quotients cannot be dismissed on the grounds they are conservative, because EPA has not established a legitimate NOAEC for birds, which may be far below 501 mg ae/kg.

XII. Risks, Costs and Mitigation

FIFRA requires that pesticides be registered only if they do not cause "unreasonable adverse effects on the environment," which includes "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."[49]

EPA has failed to provide anything close to a full and objective accounting of the risks and economic, social and environmental costs of glyphosate use. EPA acknowledges environmental risks of glyphosate use, but fails to provide any demonstration that its proposed mitigation measures would actually mitigate those risks. As discussed above, the proposed label amendments to mitigate spray drift will do little or nothing to reduce harm to terrestrial plants, including milkweed or the monarch butterfly whose existence depends upon it. Nor will the label amendments address harms to amphibians and other aquatic organisms or pollinators. EPA has not presented any assessment of the efficacy of the proposed mitigations. Without a realistic

[49] 7 U.S.C. §§ 136a(c)(5)(C); 136(bb).

assessment of mitigation measures' efficacy and feasibility, risk cannot be predicted accurately and EPA's determination is not supported by substantial evidence.[50]

Neither has EPA accounted for the many substantial costs of glyphosate use. Instead, the Agency focuses almost entirely on putatative "benefits," as evidenced in the section of the proposed interim decision entitled "Benefits Assessment" (EPA 2019, pp. 34-35), and the title of the supplemental document, "Glyphosate: Response to Comments, Usage, and Benefits" (EPA 4/18/19). In this latter document, there are multiple sections that address putative "benefits" but none in which "costs" are specifically addressed, much less accounted for in a quantitative or semi-quantative manner.

These failures to effectively address environmental risks or to account for costs renders EPA's registration review biased and incomplete, and thus inadequate to support the proposed decision under federal law.

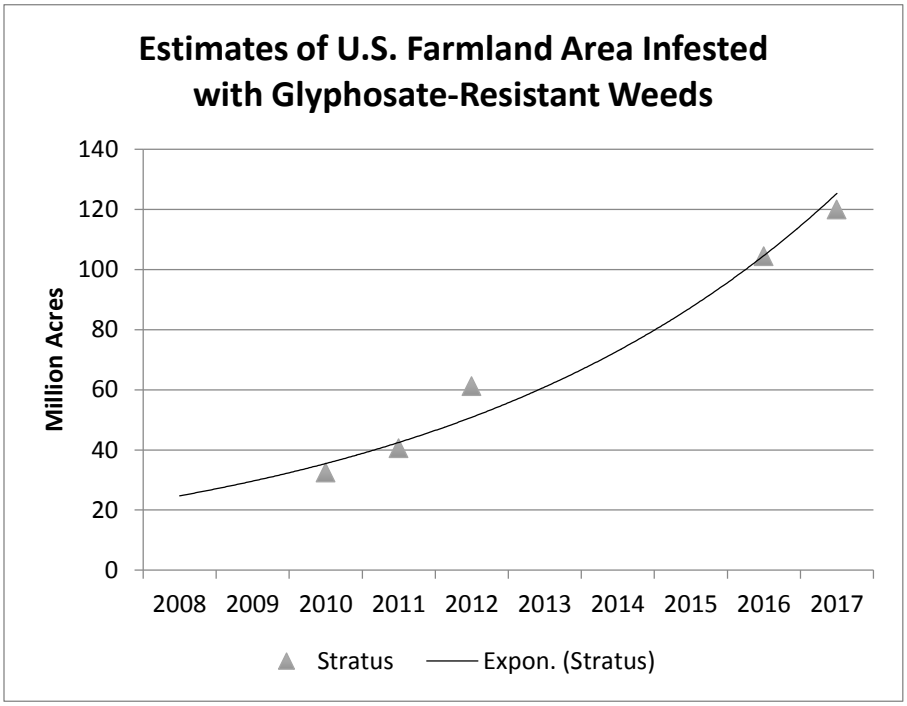
A major cost of excessive glyphosate use has been the epidemic evolution of glyphosate-resistant weeds, the great majority of which have emerged in fields planted to glyphosate-resistant (GR) crops, particularly GR soybeans, cotton, corn and sugar beets. In our comments on EPA's scoping documents for the glyphosate registration review a full decade ago, CFS provided a detailed discussion of increasing glyphosate use driven by GR crops; the developing glyphosate-resistant weed threat and associated loss in efficacy of glyphosate; the widespread introduction of follow-on crops resistant to other herbicides as a short-term fix to glyphosate resistance that would drive large increases in use of these additional herbicides, such as dicamba and 2,4-D; and the resulting harms to U.S. agriculture, human health, and the environment entailed by these developments (CFS 2009). EPA failed to take any action to address these threats.

The graph below shows the exponential increase in GR weeds in the U.S., with a near-quadrupling of infested land area – from 33 to 120 million acres of farmland – from just 2010 to 2017. In a 2017 survey of 4,000 growers, 73% report glyphosate-resistant weeds in their fields (Pucci 2018).

Farmers bear substantial additional costs to control these weeds, including increased expenditures on additional herbicides and increased use of soil-eroding tillage (USDA ERS 2015). For instance, in 2013 agronomists estimated that glyphosate-resistant weeds had increased farmers' herbicide expenditures by six-fold in both Arkansas cotton (from $50-75 to $370 per hectare) and Illinois soybeans ($25 to $160 per hectare) (Service 2013). Georgia cotton growers saw their herbicide costs double with the rapid spread of glyphosate-resistant Palmer

[50] 7 U.S.C. § 136n(b).

amaranth, to pay for additional weed-kiilers such as paraquat, glufosinate and residual herbicides, which proved insufficient for many; so they also spent far more on hand-weeding crews and for increased tillage operations (Sosnoskie and Culpepper 2014). Increased tillage to control GR weeds increases soil erosion, a significant cost of glyphosate. These are just a few of many examples that could be cited. The response to GR weeds is a major factor driving the 34% increase in agricultural herbicide use from just 2005 to 2012 (EPA 2017). For instance, Monsanto's dicamba-resistant soybeans and cotton increased overall dicamba use on these crops to nearly 10 million lbs. in 2018, just their second season of broadscale planting, an amount roughly 12-fold greater than was used, on average, from 2012 to 2016 (EPA 11/1/18). Because these crop systems were specifically introduced to control weeds resistant to glyphosate and other herbicides, the millions of acres of crops damaged as a result of dicamba drift represent a significant cost of U.S. agriculture's glyphosate addiction.



Based on data from Stratus Ag Research in: Fraser (2013) and Pucci (2018).

These higher costs are borne not only by farmers whose glyphosate use with glyphosate-resistant crops triggered the rapid evolution of resistant weeds, but also by other farmers. This is because once a glyphosate-resistant weed population has emerged, gene flow can spread the resistance to other weeds of the same species via cross-pollination, or to new areas via long-distance travel of weed seeds bearing the glyphosate-resistance trait (Dauer et al 2009, Webster and Sosnoskie 2010, Beckie et al 2019). This has been described as a "tragedy of the commons" dilemma, in which a common resource (weed susceptibility to glyphosate) is squandered for all.

A second costly consequence of the glyphosate-resistant weed epidemic has been massive adoption of crops genetically engineered for resistance to dicamba, and the associated huge increase in its use to control GR weeds. Volatile and drift-prone, intensive and extensive use of dicamba on dicamba-resistant soybeans and cotton has caused drift damage to millions of acres of non-dicamba-resistant crops, including destructive damage to susceptible vegetable farms and fruit orchards, substantial yield loss for many farmers, as well as considerable environmental damage (e.g. Unglesbee 2018).

EPA provides absolutely no accounting of these or other costs in its proposed interim registration review decision. EPA fails to even provide basic information on the area of cropland infested by GR weeds. EPA's response to weed resistance is to tout two Pesticide Registration Notices (PRNs). One "promotes mechanism of action labeling by pesticide registrants." The second provides guidance for managing herbicide resistance (EPA 4/18/19, pp. 8-9). These responses are ridiculously inadequate. Most herbicide labels have long listeded mechanism of action information, and the guidance on herbicide resistance management reiterates ineffective measures long promoted by agronomists, which the continuing rapid evolution of weeds resistant to glyphosate and other herbicides demonstrates are ineffective (Mortensen et al 2012). EPA makes no attempt to assess the efficacy of these PRNs, because if it did, it would find them to be useless.

Neither has EPA accounted for the costs of glyphosate drift, despite acknowledging that glyphosate drifts at plant-damaging concentrations well beyond the edge of sprayed fields, and evidence showing it to be among the leading herbicides implicated in drift episodes (AAPCO 1999, 2005).

EPA has not accounted for the many social, economic and environmental costs of glyphosate use, and therefore cannot lawfully issue a final registration review decision.

Respectfully submitted,

/s/
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Center for Food Safety

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