July 24, 2017
VIA ELECTRONIC MAIL

The Honourable Jane Philpott
Minister of Health
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Ottawa, ON, K1A 0K9

Dear Minister Philpott,

Re: Final Notice of Objection to Re-evaluation Decision RVD2017-01, Glyphosate, April 28 2017

Équiterre, David Suzuki Foundation, Canadian Association of Physicians for the Environment, Environmental Defence and Prevent Cancer Now are filing a Notice of Objection to the Re-evaluation Decision RVD2017-01, Glyphosate, announced on April 28, 2017 (hereafter referred to as "Decision"). This Notice of Objection is pursuant of subsection 35(1) of the *Pest Control Products Act* (PCPA), and consists of this letter and attached appendices listed below. **This Notice of Objection replaces our previous submission on June 24, 2017**.

The previous submission was made upon request by the PMRA to submit a Notice of Objection within the 60 day period after the Decision was made, despite the fact that they were not able to grant timely access to the Reading Room because their application forms were not made publicly available in a timely fashion. The groups have now had access to the Reading Room and are able to submit a complete Notice of Objection.

The Notice of Objection is being filed on the grounds that the PMRA has failed

to consider and has dismissed critical evidence in its Decision, with regards to the following risks of glyphosate:

- failure to consider critical evidence about glyphosate's impact on milkweed and monarch decline
- failure to consider critical evidence associated with glyphosate's impact on microbiomes - both human and in the soil
- failure to consider critical evidence associated with glyphosate's health impacts, including cancer
- failure to evaluate roles of glyphosate as a chelator, in both soil depletion, and in mobilization of the neurotoxic carcinogen cadmium in grains

Also, the PMRA has failed to consider evidence and has failed to acknowledge critical knowledge gaps in the following risk management strategies included in the Decision:

- failure to consider evidence that demonstrates that riparian buffer strips and buffer zones are inefficient as risk management strategies, particularly concerning efficacy, environmental persistence, and risks to groundwater and surface water contamination
- failure to consider some evidence that shows that labelling may not be an effective strategy to manage risk, and failure to acknowledge large knowledge gaps in the evidence on the efficacy of labelling to manage risks

Because the Decision 1) did not consider or dismissed critical evidence when evaluating the risks posed by glyphosate, and 2) did not consider all evidence and did not acknowledge significant knowledge gaps in the efficacy of risk management strategies, the PMRA's re-evaluation is flawed. Furthermore, the PMRA's process of review is flawed because it lacks systematic review and methodological rigour.

Based on this, the Minister cannot determine that glyphosate does not pose unacceptable risks to individuals and the environment as required by the primary objective of the PCPA, 4(1). The Decision should be reviewed by an independent review panel established by the Minister pursuant to section 35(3) of the PCPA.

Attached to this letter are the following documents:

1. Completed forms entitled “Health Canada Notice of Objection under Subsection 35(1) of the Pest Control Products Act” on behalf of each organization filing this Notice of Objection
2. A report prepared by the organizations and scientific advisors that presents the scientific grounds for the Notice of Objection

Sincerely,

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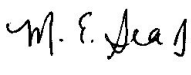

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Scientific Grounds for the Notice of Objection

A. EVIDENCE OF RISKS

1. Failure to consider critical evidence that associates glyphosate with milkweed and monarch decline

The Committee on the status of Endangered Wildlife in Canada (COSEWIC) listed the monarch as a species of "Special Concern" in 1997 and upgraded it to "Endangered" in 2016.

The persistent decline of monarch populations is multifactorial (see Table 1 from Inamine et al. 2016), and includes habitat loss. Of particular concern to the PMRA should be the effects of glyphosate on milkweed, necessary for the monarch's spring and summer breeding, and on flowering plants which produce nectar, necessary for fall migration.

Table 1. Proposed threats to eastern monarch populations

Proposed threat	References
Habitat destruction/logging at the overwintering sites	Malcolm 1993, Brower et al. 2012b, Vidal et al. 2014
Habitat destruction/reduced nectar availability on southern migration	Alonso-Mejía et al. 1997, Brower et al. 2006
Disease, predation, and parasitoids	Bradley and Altizer 2005, Oberhauser et al. 2015
Climate change/extreme weather	Oberhauser and Peterson 2003, Brower et al. 2012b
Herbicides/genetically modified herbicide tolerant crops (loss of milkweed)	Zalucki and Lammers 2010, Pleasants and Oberhauser 2013, Flockhart et al. 2015
Insecticides/genetically modified insecticidal crops	Krischik et al. 2014
Automobile accidents, especially during the migration	McKenna et al. 2001
Electromagnetic fields/microwave emissions	Guerra et al. 2014
Trap plants	Casagrande et al. 2014, Batalden and Oberhauser 2015

It is acknowledged that glyphosate's intended use is to kill weeds, including milkweed, in agricultural fields, but the PMRA has failed to adequately evaluate broader ecological effects of milkweed decline, including the links between intensive glyphosate use, milkweed decline, nectar availability from flowering plants, and monarch populations. As a result, the PMRA has failed to integrate necessary mitigation strategies in its Decision to protect the monarch butterfly.

Though the PMRA states that glyphosate is not supposed to destroy monarch habitats (including milkweed) outside of field limits (p.47, PMRA 2017), scientific evidence suggests that limitations on glyphosate use within a) agricultural regions and b) along roadsides is necessary to protect the viability of monarch populations.

Despite a vast and growing body of literature on glyphosate, milkweed, flowering plants and monarch decline, the PMRA staff indicated that they only considered 4 peer reviewed sources related to milkweed and monarchs in their decision. These sources are either a) limited in their conclusion or b) provide suggestions that the PMRA does not follow in their process of evaluation and final decision to mitigate risk. These include:

1) Boutin et. al. (2004), which did not assess glyphosate toxicity on milkweed;

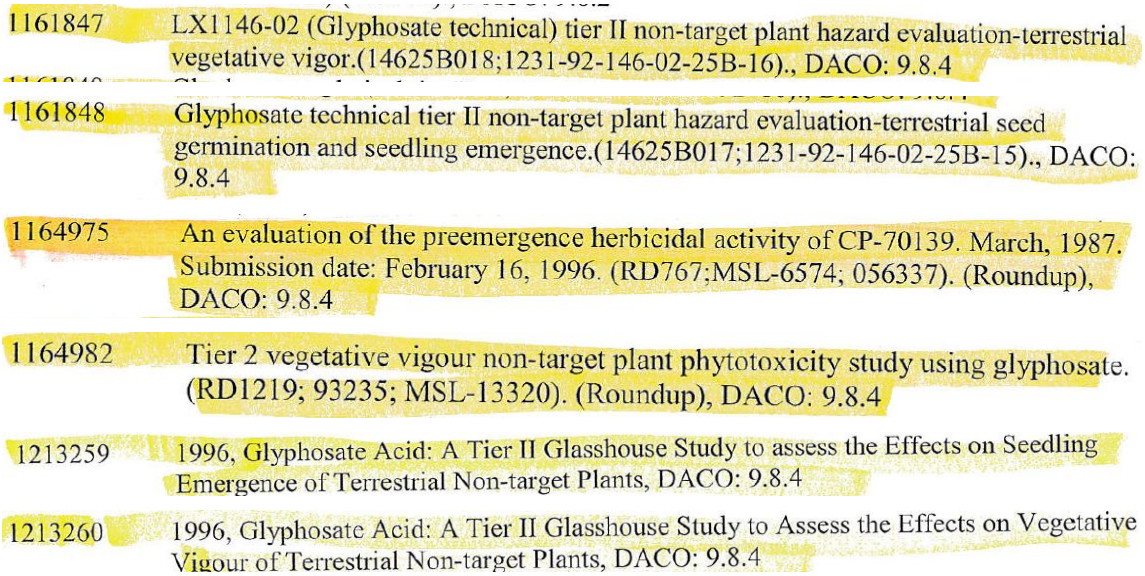
2 and 3) White and Boutin (2007) and Wyrill and Burnside (1977), which both indicate that additives in glyphosate-based formulations increase toxicity to non-target plants, but the PMRA has failed to evaluate surfactants and formulations

4) USEPA (1993), which suggests the need for labelling requirements for endangered species to mitigate risks, which the PMRA not consider and furthermore, the efficacy of labelling to mitigate risk must be questioned (see section B.2. below on the efficacy of labelling).

Please see Appendix 1 for a more extensive synopsis of theses studies and the assertions made above. In brief, these studies suggest that:

- Milkweed should be added to the plant list that is assessed for toxicity in pesticide registration.
- Glyphosate alone and in a wide variety of formulations should be tested in greenhouse settings on milkweed to assess lethal concentrations, chronic toxicity, impact of seed germination and re-growth from rhizomes.
- Environmentally realistic herbicide concentrations related to aerial spray drift and runoff to milkweed habitats along roadsides or field margins should be tested, to ensure tha use in these targeted areas does not negatively affect milkweed and monarchs in their preferred habitats.

PMRA's staff and technical experts also cited 6 sources included in the Confidential Business Information accessed through the reading room, that they affirmed considered glyphosate's impact on milkweed and monarchs. These include the following 6 sources:



1161847	LX1146-02 (Glyphosate technical) tier II non-target plant hazard evaluation-terrestrial vegetative vigor.(14625B018;1231-92-146-02-25B-16)., DACO: 9.8.4
1161848	Glyphosate technical tier II non-target plant hazard evaluation-terrestrial seed germination and seedling emergence.(14625B017;1231-92-146-02-25B-15)., DACO: 9.8.4
1164975	An evaluation of the preemergence herbicidal activity of CP-70139. March, 1987. Submission date: February 16, 1996. (RD767;MSL-6574; 056337). (Roundup), DACO: 9.8.4
1164982	Tier 2 vegetative vigour non-target plant phytotoxicity study using glyphosate. (RD1219; 93235; MSL-13320). (Roundup), DACO: 9.8.4
1213259	1996, Glyphosate Acid: A Tier II Glasshouse Study to assess the Effects on Seedling Emergence of Terrestrial Non-target Plants, DACO: 9.8.4
1213260	1996, Glyphosate Acid: A Tier II Glasshouse Study to Assess the Effects on Vegetative Vigour of Terrestrial Non-target Plants, DACO: 9.8.4

However, upon a thorough review, none of these studies made any reference to monarchs or milkweeds, nor included an evaluation of effects of glyphosate on either. It is concerning that the technical experts on the Decision would not know what is or isn't included in sources referenced in the Decision.

Taking both the public and confidential sources together, the PMRA's Decision is therefore deeply flawed in that it does not take into consideration a vast and growing body of literature that demonstrates glyphosate's impact on milkweed and monarchs. A more thorough literature review is summarized below to reveal, on scientific grounds, the gaps in the PMRA's evaluation process.

a) Milkweed decline in agricultural regions affect monarch spring and summer breeding grounds

In its northern ranges, the monarch butterfly (*Danaus plexippus*) depends on the common milkweed (*Asclepias syriaca*) for survival. *A. syriaca* generally grows in open habitats, but has suffered massive declines particularly across corn and soy growing regions (Commission for Environmental Cooperation 2008; Brower et al. 2012a; Millet et al 2012; Pleasants and Oberhauser 2012; Flockhart et al. 2013, 2015; Center for Biological Diversity 2014; Jepsen et al. 2015, Zaya et al. 2017). Across the corn and soy belt in the United States midwest, declines in *A. syriaca* have been measured at 81% (Pleasants, 2013)

and more recent studies show even more pronounced losses between 93.7% and 96.5% (Zaya et al. 2017).

Zaya et al. (2017) describes the relationship between milkweed decline and the increased use of glyphosate in corn and soy production:

> *"Because milkweeds are highly susceptible to glyphosate herbicides, the connection between A. syriaca declines and glyphosate use is thought to be causal… Supporting the causal role of glyphosate-treatments in these declines, milkweed abundance in two soy fields with a single glyphosate application declined by more than 70% over the season, whereas non-glyphosate treatments in both corn and soy had small to little effect on milkweed abundance (box 1; Pleasants 2015)." (p.2)*

Milkweed losses as a result of increased glyphosate use in corn and soy production regions are a major contributor to monarch declines, as described by Jepsen et al. (2015):

> *"increased use of the herbicide glyphosate and its detrimental effect on milkweed is almost certainly playing a significant role in the monarch population decline. This impact is magnified as huge amounts of habitat have been – and continue to be – converted to glyphosate-impacted croplands." (p.26)*

Several authors reach similar conclusions, and some even state that increases in glyphosate use on herbicide-tolerant crops may eventually lead to the complete disappearance of milkweed in agricultural regions with very consequential effects for monarch populations. For instance, whereas a survey conducted in 1999 of habitats containing a particular milkweed species showed that the number of monarchs produced per hectare (ha) in corn and soy field was as high or higher than that of other habitats (Oberhauser et al, 2001), the rapid adoption of genetically modified glyphosate resistant soy and corn crops after 1999 led to a significant reduction of milkweed and reduced fecundity in monarch females:

> *"Much of the combined acreage of soya and maize (60–70 million ha per year) is used in rotation, and this*

> *rotation in combination with the high adoption rate of GR (genetically resistant) soya (>70% by 2002, presently 92%) and maize (presently 23%) (U.S.D.A., 2010a) has all but eliminated A. syriaca from 40 million ha of these croplands (Taylor, 2008). Both Hartzler (2010) and J.M. Pleasants (in prep.) have documented the drastic reduction of A. syriaca growing in glyphosate-treated fields in Iowa; Hartzler recorded a 90% loss from 1999 to 2009, and Pleasants measured a 79% loss from 2000 to 2009. We conclude that, because of the extensive use of glyphosate herbicide on crops that are genetically modified to resist the herbicide, milkweeds will disappear almost completely from croplands. Furthermore, Zalucki and Lammers (2010) have estimated with models that the large-scale elimination of milkweeds in agricultural and surrounding landscapes has the effect of increasing the search time for host plants by monarch females with the result that realized fecundity is reduced. '' (p.3 Grower et al. 2012)*

These continental trends suggesting glyphosate's impact in milkweed decline and subsequent impacts on monarch populations have recently been confirmed at the regional scale. Based on evidence of monarch populations and estimates of the application of glyphosate in corn and soy fields, Saunders et. al. (2017) provides:

> *"...the first empirical evidence of a negative association between county-level glyphosate application and local abundance of adult monarchs, particularly in areas of concentrated agriculture."*

This decline in monarch counts and glyphosate applications is particularly sharp over the first few years of adoption of glyphosate resistant crops (Figure 1a) 1994-2003 vs b) 2004-2013).

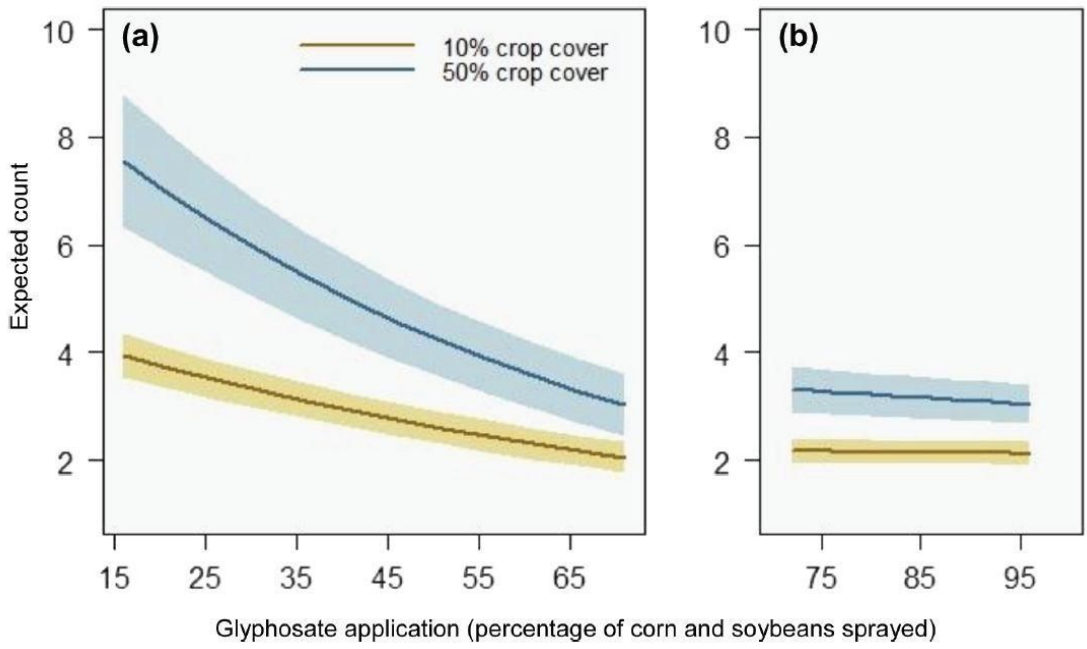


Figure 1 Expected monarch counts declining with increasing glyphosate application, extracted from Saunders et al. 2017.

Because ‘’each milkweed stem in an agricultural field averages 3.9 times more monarch eggs than a milkweed stem in non-agricultural habitats’’ (Pleasants et al. 2017), such significant and precipitous declines in milkweed in agricultural lands is concerning. Pleasants et. al. (2017) argues that between 425 million to 1.6 billion milkweed plants in the monarch breeding grounds would be necessary to reach monarch conservation goals, which means that glyphosate use restrictions in Canada are urgent. Because the PMRA failed to consider this critical evidence making the link between increased glyphosate use, milkweed declines, and monarch declines, the PMRA has failed to propose appropriate risk mitigation strategies to protect monarchs and monarch habitats in its Decision.

Buffer strips are often suggested as habitat protection areas because they support mid-cycle vegetation in corn and soy production regions. However, a recent study in Québec on the effectiveness of riparian buffer strips in protecting biodiversity demonstrated that *A. Syriaca* was not observed on the side of the buffer strip close to the agricultural field but was observed on the center of the buffer strip and on the edge of the stream, where it has an increased chance of being sheltered from glyphosate (Hénault-Ethier, 2016).

This research shows that buffer strips could harbour some milkweed to support monarch populations in agricultural areas, but suggests that these habitat protection areas may not be sufficient to support large populations of milkweed to re-invigorate monarch populations. An enlarged no spray buffer zone before the riparian buffer strip could better protect important, marginal milkweed habitat for monarch summer breeding grounds in agricultural regions.

b) Reduced availability of nectar along roadsides affects fall migration

Beyond protecting summer breeding grounds, recent research suggests that sparse autumnal nectar sources in the monarch northern ranges may also be a primary driver for monarch declines (Inamine et al. 2016). Whereas milkweed is essential for monarch breeding in the spring and summer, nectariferous flowers are critical in the fall for transition and migration to overwintering grounds in Mexico. Not only are the "... conditions of the fall migrants … affected by the environment they experience early in life, including milkweed shortage, insecticides, or other changes in habitat quality" (Inamine et al. 2016), roadside maintenance in Canada involves herbicide spraying which limits nectar-producing flowering vegetation along crucial corridors. According to Environment and Climate Change Canada (ECCC) (2014):

> *"The removal of nectar-producing, flowering vegetation along roadsides is a potential threat for the Eastern population of Monarch. For example, mowing, cutting, and spraying of herbicides on roadside vegetation in southern Ontario are standard practices" (p.17)*

ECCC's Monarch management guidelines recommends reducing the widespread use of herbicides along roadsides.

> *''Develop and implement roadside, power line and railway maintenance guidelines or best management practices that conserve and enhance Monarch breeding and nectaring habitat and communicate those with appropriate sectors. These should be regionally and context specific to address timing requirements, invasive species present, species of Milkweed native*

to that region, and the nature of activities.'' (p.24 Environment Canada, 2014)

The PMRA's Decision has failed to develop use limitation guidelines consistent with ECCC's monarch management plan. At the very least, the PMRA must integrate the recommendations in the proposed monarch management plan 2014-2019, and cannot defend continued inaction on risk mitigation strategies by calling for further research, especially when strategies have already been proposed by other federal Ministries in Canada.

2. **Failure to consider critical evidence associated with glyphosate's impact on microbiomes -- for humans and in the soil-- as a patented antibiotic**

Glyphosate is registered as a patented antibiotic and may have adverse effects on microbiomes in different environments, both in the human body and in the soil. The PMRA's Decision indicated that effects on the microbiome are beyond the scope of pesticide assessment – either the human microbiome that may directly modulate the risks of cancer and other adverse outcomes, or the soil microbiome and increases in moulds and fusarium toxin – that may also contribute to cancer and other adverse conditions for human health and crop productivity.

Scientists from around the world are urging regulatory bodies to conduct thorough and modern assessment of glyphosate-based herbicide toxicity to encompass impacts on the gut microbiome (Peterson Myers, J., 2016) and state that "current safety standards for glyphosate-based herbicides are outdated and may fail to protect public health and the environment'' (Vandenberg, Blumberg et al. 2017). Canada's regulatory body is falling behind while other jurisdictions take into account glyphosate's impact on microbiome: for instance, the EU conditionally requires additional microbiological tests, for example, on soil nitrogen transformation and various formulations' effects on microflora (European Commission, 2013, vol. 283 and 284).

No justification was given for why the PMRA did not take into account glyphosate's impacts on microbiomes. This is particularly unacceptable, not only because the anti-microbial effects of glyphosate-based herbicides are patented and widely reported in the scientific literature, but also because the PMRA cites Confidential Business Information sources that show potential impact on the

microbiome, and that these effects have relevant implications for major chronic diseases. These same diseases are increasing rapidly in Canada (Elmslie 2012). The PMRA's re-evaluation must be comprehensive and must include a thorough review of glyphosate's impact on microbiomes, and in this vein, outlined below is some of the evidence on glyphosate's impact on microbiomes.

a) Human microbiome

There are epidemiological correlations between glyphosate and several modern day diseases which warrant a better understanding of glyphosate on the gut microbiome (Swanson, Leu et al. 2014). There are strong correlations between escalating glyphosate use and increases in diabetes prevalence (R=0.971), obesity (R=0.962), autism (R=0.960), inflammatory bowel disease (R=0.938), and many others. Several diseases correlated with glyphosate may be related to sub-optimal, albeit modifiable microbiome. The Canadian Cancer Society reported in 2017 that colorectal cancer is increasing rapidly in younger adults (below 50 years of age). Dysbiosis causes increased inflammation, that may lead to cancer in the inflamed tissue (Goodson et al., 2015).

Correlations between glyphosate and diseases are insufficient to prove harm. Direct evidence in animals and mechanistic studies in laboratory settings are essential to assess whether glyphosate has an effect on mammalian gut microbiome. Nonetheless, glyphosate is already known to selectively affect bacterial populations *in vitro* (Kurenbach, Marjoshi et al. 2015). We may not yet have sufficient evidence to associate glyphosate with celiac disease as claimed by Samsel and Seneff (2013). However, exposure to increased levels of pollution could be crucial in gut microbiome alterations which may lead to gastrointestinal disorders (Zhang, Nichols et al. 2015). Inflammatory bowel diseases have dramatically increased with the ‘’Westernization’’ of diets (Konkel 2016). Glyphosate is currently considered by several regulating bodies as one of the least toxic pesticides, but critical gaps in its evaluation need to be filled before we can really conclude on its safety (Myers, Antoniou et al. 2016).

Thus, given these implications, it is unclear why PMRA did not request additional data on animal gut microbiome alterations associated with glyphosate to inform its decision making process. Diarrhea and other signs of intestinal distress currently not considered to be “adverse” in animal studies

warrant further studies.

It is well known that stool consistency is associated with gut microbiome composition, and may be a marker in studying animal health. “The strength of the associations between stool consistency and species richness, enterotypes and community composition highlight the crucial importance of stool consistency assessment in gut metagenome-wide association studies.’’ (Vandeputte, Falony et al. 2016). Using stool consistency as an indicator of gut microbiome alterations, a review in the Reading Room of the animal data that was highlighted to be central in the final decision by the PMRA technical experts revealed potential effects on human health microbiome. These are worth studying in greater depth, with a sensitivity analysis of the final decision and limits for glyphosate in food. Indeed, the majority of studies the PMRA highlighted for review in the reading room show potential effects on the microbiome (Table 1).

Table 1 : Evidence for potential microbiome effects in animal studies found in unpublished studies.

PMRA Study Number	**Date**	**Type of study**	**Suggestive evidence for impact on microbiome?**	**Key findings**	**Dosage**
1126903	1993	Developmental toxicity of AMPA in rats oral exposure	Yes	Soft stool, mucoid feces	400 & 1000 mg/kg/day
1161752	1991	Acute oral toxicity study on rats with N-methyl-N-phosphonomethyl glycine oral exposure	Yes	Diarrhea in 4/10 rats on day 2	1000 mg/kg/day

11617 53	1994	Acute oral toxicity of AMPA on 10 rats	Yes	Diarrhea, subdued behavior, haunched appearance, soiled anal & perigenital areas within 4h to 3d after dosing.	5000 mg/kg bw/day
11617 68	1991	4 weeks dietary toxicity study in rats using 99,5% pure glyphosate	Yes	Soft Stool during weeks 3 and 4 at high doses	0,50,250,10 00 & 2500
11617 79	1991	Effect of glyphosate on pregnancy in rabbit	Yes	Gastro-intestin al disturbances At 450 dose, prior to death, reduced food intake & body weight loss observed. At 150 and 450 dose, parents expressed gastrointestinal disturbances.	50, 150 & 450 mg/kg/day
11617 88	1990	Oral toxicity in dogs (99,5% glyphosate powder administered in capsules daily for 52 weeks)	Yes	Faecal consistency changed (soft, loose or liquid feces) recorded frequently for high dosed animals	0,30, 300 & 1000 mg/kg/day
11847 27	1980	Dutch belted rabbits	Yes	Soft stool & diarrhea (none at 75, slight increase at 175 and definite increase + nasal discharge at 350 dose)	75, 175, 350 mg/kg/day

12120 11	2001	Rats dosed orally (food)	No	None obvious	0, 2000, 6000, 20000 ppm (nominal) Males: 1,121, 361, 1214 mg/kg bw/day and Females: 0, 145, 437 & 1498 mg/kg bw/day
12120 12	2001	Continuation of above study	Continuatio n of above	Same	Same
12120 13	2001	Continuation of above study	Continuatio n of above	Same	Same
12120 34	1996	Acute neurotoxicity in 20 rats administered single oral doses	No	None obvious	0,500,1000 & 2000 mg/kg bw/day
12120 35	1988	Aminomethyl phosphonic acid assessed for acute oral toxicity in 10 rats at 5000 mg/kg bw/day	Yes	Diarrhea, sign of diarrhea in days 1,2,3,4	5000mg/kg/ day
12353 39	1990	2 generations of rat reproduction study (diet, 11 weeks)	Yes	Soft Stools in high doses males & females	0, 2000, 10 000 & 30 000 ppm

b) Soil microbiome

The PMRA failed to consider evidence of the effects of glyphosate on soil microbiomes and has not imposed risk mitigation and reduction strategies necessary to protect the soil microbiota, while indicating that this topic is beyond the scope of pesticide assessment (section 2.2.3). This is contrary to

the most recent understanding of the importance of soil microbiome on plant and soil health. Neglecting such aspects may lead to eventual yield reductions as there may be alterations in diseases and nutrients available in the fields.

Glyphosate's herbicidal activity relies on inhibition of aromatic amino acid biosynthesis. The safety assumed because humans cannot synthesize aromatic amino acids in the first place provides a narrow, incomplete understanding of this essential pathway in the environment, especially on soil and crop health. Microorganisms too rely on the shikimate pathway for the synthesis of aromatic amino acids. Reports of adverse effects of glyphosate on individual microbial species and communities are abundant (see for example (Kremer and Means 2009; Zobiole, Kremer et al. 2011) and other references listed in (Aristilde, Reed et al. 2017)). *Pseudomonas* species produce various antibiotic compounds, siderophores and plant growth promoters. For this reason, they have been employed as effective biocontrol agents to protect plants against pathogens and promote plant health (Timmis 2002). Different bacterial species including *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* or the Nitrogen fixing *Azotobacter chroococcum* and *A. vinelandii* may exhibit different lethal doses or different adverse metabolic effects at different glyphosate concentrations (Santos and Flores 1995; Duke, Lydon et al. 2012).

Repeated glyphosate application results in a shift to fungal species breaking down plant material, and with this a serious increase in aflatoxins. Arnason (2017) recently reported that aflatoxin problems are escalating among farms that use synthetic pesticides on grains but are a rarity among organic farms. The solution to aflatoxin contamination has perversely been to increase spraying of glyphosate pre-harvest, to encourage more rapid dry-down.

Soils in organic agriculture typically contain more carbon and a greater diversity of bacterial species that break down organic matter. This observation is frequently made by farmers converting from agriculture that is highly dependent on synthetic pesticides, including glyphosate (Lynch 2009).

Rhizosphere bacterial communities are known to shift during long term exposure to glyphosate in corn and soy (greenhouse experiment) (Newman, Hoilett et al. 2016). Next generation sequencing of rhizospheric soil shows an

increase in *Proteobacteria* (particularly gammaproteobacteria) and a decrease in *Acidobacteria* in response to glyphosate exposure. These latter bacteria are involved in biogeochemical processes, thus their decrease could impact the nutrient status of the rhizosphere. Hence, '' A comprehensive understanding of the responses of the entire rhizospheric microbiome is required to assess fully the non-targeted metabolic effects of glyphosate on crop-beneficial microbial communities.'' (Aristilde, Reed et al. 2017).

Furthermore, glyphosate can also affect gene expression in soil bacteria, downregulating carbon metabolism and amino acid synthesis and upregulating protein metabolism (Newman, Lorenz et al. 2016). ''Glyphosate-induced specific disruption of de novo biosynthesis of aromatic AAs accompanied by widespread metabolic disruptions was responsible for dose-dependent adverse effects of glyphosate on sensitive soil *Pseudomonas* species.'' (Aristilde, Reed et al. 2017). Thus glyphosate not only changes the soil microbial communities; it also changes their activities.

3. **Failure to consider critical evidence associated with glyphosate's impact on human health, including cancer**

a) Cancer

Our analysis of the final decision document indicates that the PMRA did not include statistically significant cancer findings in its assessment of the carcinogenic potential of glyphosate. Only one of many epidemiological studies was included (the US Agriculture Health Study), and none of the publications from a large, federally-funded cross-Canada case-control study of pesticides and non-Hodgkin Lymphoma were referenced or identified by the PMRA (Initial report: McDuffie H, et al., 2005).

The most recent exchanges in the glyphosate carcinogenicity conversation in the peer-reviewed literature is the Portier and Clausing response to the Tarazona et al. review of the confidential data considered in Europe, that was recently made public.

Dr. Christopher Portier is the former Director at the US National Center for

Environmental Health; former Director at the US Agency for Toxic Substances and Disease Registry; former Associate Director as the US National Institute of Environmental Health Sciences; former Associate Director at the US National Toxicology program; and a fellow at the American Statistical Association and the International Statistics Institute.

Dr. Portier analyzed raw data from animal cancer studies considered in the European evaluation of glyphosate, that was confidentially released to selected scientists under a public access request. The analysis was summarized in an open letter dated May 28, 2017, to the President of the European Commission, Jean Claude Juncker. Portier details 7 newly revealed animal studies beyond those previously considered, where significant pairwise comparisons or trends indicated carcinogenicity for 8 tumour types.

Dr. Portier found eight *"significant increases in tumor incidence that do not appear in any of the publications or government evaluations presented by both EFSA and EChA".* According to Dr. Portier, *"Some of these tumors were also present in multiple other studies increasing the consistency of the findings across studies."* For Dr. Portier, this *"suggests that the evaluations applied to the glyphosate data are scientifically flawed, and any decisions derived from these evaluations will fail to protect public health."* The PMRA relies on the EFSA's finalized re-assessment of glyphosate in the Glyphosate Re-evaluation Decision but does not note the underlying scientific flaws identified by Dr. Portier.

Dr. Portier asks *"that the evaluations by both EFSA and EChA be repeated for all toxicological endpoints and the data underlying these evaluations be publicly released."* Portier also identified 13 other statistically positive findings for tumor sites.

From these 21 studies of glyphosate identifying positive tumor findings, the PMRA only included 3 as shown by the comparison table below (Table1).

Table 1

Reference	Taken into account in the PMRA assessment*	PMRA response
Atkinson, C., Strutt, A., Henderson, W., et al. (1993a). 104- Week Chronic Feeding/Oncogenicity study in rats with 52-week interim kill. MRID No. 49631701. Unpublished	YES	REJECTED CONCLUSIONS
Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993b). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702. Unpublished.	YES	REJECTED CONCLUSIONS
Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Wistar Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. MRID 49704601. Unpublished.	YES	REJECTED CONCLUSIONS

Enemoto, K. (1997), HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 1. The Institute of Environmental Toxicology, Kodaira-shi, Tokyo, Japan, Arysta LifeSciences, Study No.:IET 94-0150. MRID 50017104, 50017105, 5001703. Unpublished.	NO	Not applicable
Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011.EPA Accession No. 251007 – 251009, and 251014. EPA Accession no. 251007-09, 251014. Unpublished.	NO	Not applicable
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Wood, E., Dunster, J., Watson, P., and Brooks, P. (2009a) Glyphosate Technical: Dietary Combined Chronic Toxicity/Carcinogenicity Study in the Rat. Harlan Laboratories Limited,Page 156 of 227 Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK.	NO	Not applicable

Wood, E., Dunster, J., Watson, P., and Brooks, P. (2009b) Glyphosate Technical: DietaryCarcinogenicity Study in the Mouse. Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. Unpublished.	NO	Not applicable

* *It may be that some of these studies are included in the PMRA's re-evaluation decision as unpublished references, but it is difficult to compare without complete identifiable bibliographic reporting by the PMRA, even after a review of the documents that the technical team of PMRA provided for consideration in the Reading Room.*
* *The PMRA re-evaluation does not note why some of the studies in Table 1 were dismissed, but it is possibly because the NOAELs are above those used in the Glyphosate re-evaluation. If so, this is inappropriate because higher doses are routinely used to improve the likelihood of detecting the effect in relatively small numbers of animals over a shorter life-span. As well, cancer is frequently considered a non-threshold outcome, so all evidence should be included and considered, preferably in a meta-analysis.*

It is not feasible to correlate the studies critiqued by Portier with corresponding PMRA studies, but it appears that the PMRA was not provided with a complete data set, and/or analyses were incomplete, and/or selection was biased towards studies reporting no effects.

Dr. Portier also indicates his concerns, "that other areas of the EFSA review (e.g., reproductive toxicity and endocrine disruption) may have also received inadequate evaluations. Since the industry-supported scientific evidence is not available to external scientists, I am unable to evaluate these data and

determine if there are positive findings that escaped detection. I encourage you to release these data for external analysis and review as well." Importantly, Dr. Portier was provided with complete data for analyses. This is far greater access than provided in the Reading Room, where the PMRA made the decision that no electronic access or analytical capabilities were to be permitted.

For this review, PMRA staff highlighted by hand some studies in the PRVD2015 reference list, and provided a scanned copy, with those highlighted in green (below) pertaining to cancer outcomes. These include:

- 1 U.S. human epidemiological study of agricultural workers (Canadian studies of glyphosate applicators were excluded, and not mentioned specifically)
- 17 laboratory studies of genotoxicity
- 6 apparently unique animal studies (there were multiple reports of single studies)

This selection stands in sharp contrast to the extensive body of research considered by IARC and by other regulators. No supplementary or confirmatory references in the 2017 decision document were indicated as being central to the decision. Several of the reports are reviews of cancer and genotoxic outcomes.

In addition, the unpublished studies considered by PMRA are out of date, ranging from 1981 to 2001, according to the subset of cancer-related studies highlighted by the PMRA technical experts. As much of the carcinogenic evidence in the peer reviewed literature, and the debate surrounding potential carcinogenicity, is recent, the PMRA must revisit the more recent evidence before drawing a conclusion on glyphosate.

In his conclusion, Dr. Portier raises several major concerns "that have not been adequately addressed in the final [European] assessments and should again be addressed appropriately. These are:

- the classification of the human evidence as "very limited" is not a valid characterization under the CLP guidelines
- both EFSA and EChA dismissed positive findings because they fell inside of the range of the historical controls (this is an improper use

of historical control evidence);

- both EFSA and EChA compared findings across different strains and different study durations to conclude that studies were inconsistent (this is not scientifically justifiable);
- both EFSA and EChA characterize the evidence for genotoxicity as negative, yet a careful review of the evidence released by EFSA and the open scientific literature suggest there are many guideline and non-guideline studies demonstrating genotoxicity." The PMRA has not noted any genotoxic potential for glyphosate.

Below are a few excerpts of the conclusions reached in unpublished studies considered by the PMRA accessed in the reading room, along with the PMRA notes as positive findings were dismissed.

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Glyphosate acid is mutagenic in mouse lymphoma assay system.

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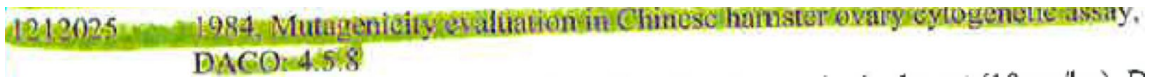
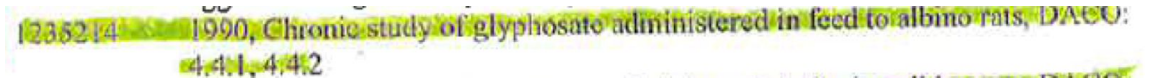


In a hamster ovary cytogenetic assay, chromosome aberrations and sister chromatid exchanges in cell cultures were detected at the lowest dose tested, but evidence was dismissed as marginal because it was not dose-dependent.

Novel scientific evidence suggests that endocrine disruption may occur in a non-dose dependent manner, and manifest itself at low doses only. Dismissal of such evidence is inappropriate based on most recent knowledge.



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In a rat dietary study, a statistically increased rate of pancreatic islet cell adenomas was observed. This result is dismissed on the basis of occurrence in historical control at the laboratory and non dose-dependent effects. The authors attribute these adenomas to spontaneous origins and unrelated to glyphosate administration.

Novel scientific evidence suggests that endocrine disruption may occur in a

non-dose dependent manner. Furthermore, this dismissal of a statistically significant finding is an inappropriate use of historic controls. Therefore, dismissal of such evidence is inappropriate based on most modern methodologies and knowledge.


1184837 1981, A lifetime feeding study of glyphosate (roundup technical) in rats, DACO: 4.4.1, 4.4.2

In a chronic toxicity and oncogenicity test of glyphosate in diets of rats, lympholytic hyperplasia in the thymus and lymph nodes of the treated group was slightly elevated compared to the control. Pathologists dismissed these lesions as being related to glyphosate treatment for several reasons, including “clear dose response was not evident.” Furthermore, interstitial cell tumors of testes in male rats was increased in all treated groups compared to control groups. This was dismissed based on recent historical control data and non-statistically significant dose-response relationship. This study suggested that it is “not unusual to find one or more statistically significant results” and interpreted these as false-positive results.
Scientific evidence indicates that endocrine disruption may occur in a non-dose dependent manner. Furthermore, this dismissal of a statistically significant finding is an inappropriate use of historic controls. Therefore, dismissal of such evidence is inappropriate based on most modern methodologies and knowledge.

Based on the Confidential Business Information available from the reading room, there is evidence that industry studies dismissed some positive results concerning cancers in animals. Various studies use different reasons to dismiss the relationship between the cancers observed and the glyphosate treatment. Some cite higher rates in historic controls; Dr Portier considered this to be improper use of historical control data. For example, in this case of the world’s most commonly used herbicide, unless historical controls were fed high quality organically grown feed they were probably exposed to glyphosate, rendering comparison with glyphosate-free controls inappropriate. Indeed, 9 out of 13 laboratory diets for rodents obtained from 5 continents contained glyphosate and AMPA residue up to 370 ppm (Mesnage, Defarge et al. 2015). Positive study results are also dismissed unless both pairwise comparisons (control animals versus animals at a particular dose), *and* trend analyses are statistically significant. Portier reinforces the point made above, that endocrine disrupting chemicals may exert greater effects at particular doses, and that monotonic dose response is not required. Other case-specific technical arguments made

by pathologists (i.e. variability, absence of dose-dependent relationship, etc.) are difficult to critique without an in depth analysis of the results with the help of a statistician, toxicologist and pathologist. Based on the improper dismissal of positive findings identified by Portier and the likely occurrence of inappropriate dismissal in the studies considered by the PMRA, an exhaustive review of the available literature, transparently addressing and reporting studies' quality and results, based on established criteria to explain why results were dismissed or incorporated needs to be conducted by the PMRA.

In comparison with other jurisdictions, the PMRA dismissed IARC's evidence of carcinogenicity on the basis that EFSA and ECHA found limited risk at common exposure levels. However not all jurisdictions agree with this decision. As of July 2017, glyphosate based herbicide manufacturers will have one year to comply with a California labelling requirement identifying glyphosate as known to the state to cause cancer. Late last year, the Netherlands banned the sale of glyphosate-based herbicides to private parties, excluding agricultural use, (AWDnews, 2017). The PMRA's flawed evaluation process does allow Canada to keep pace with the strongest regulators internationally.

b) Impact of co-formulants

From our analysis of the proposed and final decision documents, the PMRA did not assess the toxicity of commercial formulations in its re-evaluation. The PMRA states that, although the majority of toxicity studies of glyphosate on mammals have been conducted with the active ingredient (glyphosate acid), the PMRA has also examined toxicological studies that have evaluated the acute risk of preparations. The PMRA has not assessed the chronic risk of commercial formulations containing glyphosate.

Yet, the PMRA recognizes that certain studies done with commercial formulations containing glyphosate suggest that certain formulations are genotoxic, while studies that cover only the active ingredient don't reveal this adverse effect, and recognizes that this effect could be due to a component other than the glyphosate acid in these commercial formulas. Despite this acknowledgement, the PMRA claims that studies conducted with glyphosate alone are more relevant to characterize its toxicity, than studies that have been conducted on other unidentified components, the composition of commercial formulas being exclusive data to the registrant, and purportedly different from

one country to another. The PMRA states that the composition of all registered pest control products in Canada are disclosed to the PMRA and toxicity data are also required for each product that is being assessed in the pre-market evaluation process. We thus understand that the PMRA relies on data dating from the pre-market evaluation process to evaluate other components of commercial formulations. This approach risks putting aside the scientific knowledge of recent years on the adverse effects of components of commercial formulations other than the active ingredient.

This PMRA approach raises concerns, given that an increasing number of studies reveal the toxicity of other components in the commercial formulation beyond only the active ingredient. For instance, a comparison of the toxicity of different brands of glyphosate-based herbicides in tissue culture cell assays showed that several commercial formulations were up to one thousand times more toxic than glyphosate (Mesnages et. al 2014). Other studies have also demonstrated that the surfactant polyoxyethylene tallow amine (POEA), one component of the adjuvant mixture present in some glyphosate-based herbicides, was ten thousand times more cytotoxic than glyphosate itself when applied to human tissue culture cells (Mesnages et al. 2013). These results challenge the establishment of guidance values such as the acceptable daily intake of glyphosate, because these are based on tests conducted with glyphosate alone (Mesnages et al. 2013).

Although the PMRA states that it has evaluated POEA and even cites the studies mentioned above, it appears as though the PMRA didn't actually assess the toxicity of POEA. It appears that this evaluation consisted only of the acknowledgement that POEA is among formulants classified in List 4B, a list composed of formulants of minimal concern, and relied on the EPA assessment of POEA. The EPA has evaluated the risks for human health of ATAE, a sub-family of POEA, and the PMRA has examined the toxicity studies available that have been taken into account in the EPA evaluation. The EPA claims that the commercial products that contain less than 20% of POEA by weight are not of concern. According to the PMRA, all commercial products containing glyphosate currently in Canada meet this limit. The PMRA didn't present how it ensures that the EPA has taken into account all data on the subject, has taken into account the most recent results (such as the Mesnage, R., Bernay, B., et al., 2013 study mentioned before) and did a credible evaluation. Meanwhile, scientists from around the world are urging regulatory bodies to scientifically assess commercially used formulations, because herbicide mixtures likely have

effects that are not predicted by assessing glyphosate alone (Vandenberg et al. 2017; Peterson et al. 2016), as stated by Mesnage R, Defarge N, Spiroux de Vendômois J, et al. (2015):

> *"In addition, the real and various mixtures of GlyBH [glyphosate-based herbicides] to which we are exposed have not been scientifically assessed by regulatory agencies. Adjuvants (such as POEA) amplify the toxicity by increasing glyphosate uptake in cells, or by adding their own toxicity through cell membrane disruption. … The exposure of animals at doses ranging from 1 to 10 mg/kg bw per day to 5000 or even 10,000 mg/ kg bw per day during their whole life is not relevant to conclude on the effects of exposures in the range of 10-100 mg/kg bw per day. Major endpoints of toxicity for both Roundup and glyphosate, such as developmental, reproductive, transgenerational and even chronic effects on adults, still need to be investigated at relevant doses, at which endocrine disrupting effects may arise. The lack of investigation of low dose chronic effects and the neglect of non-monotonic dose-response relationships make the safety conclusions below 50 mg/kg bw/d of glyphosate questionable. The first and minimal assessment would be to test the chronic toxicity/carcinogenicity of glyphosate at its ADI over the whole life of a mammal, including a prenatal period exposure.*
>
> *"Before awaiting further mandatory and independent chronic assessment of pesticide formulations including Roundup, this large discrepancy should be borne in mind when forming policies for the protection of public health. Overall in the current regulatory assessment, any toxic effect is first suspected to be a false positive, arising by chance, rather than questioning whether no evidence of effect is a false negative result. We encourage regulators to ask for a complete re-evaluation of glyphosate formulations rather than glyphosate alone, taking into account loopholes in the current assessment."*

The NOAEL used by the PMRA for all populations and durations is 32/34 (male / female) mg/kg bw/day (chronic / carcinogenicity study in rats). It is the lowest NOAEL used by the PMRA.

We thus ask that the PMRA evaluate the chronic health impact with co-formulants included in all commercial formulations containing glyphosate registered in Canada.

c) Other health effects

A literature review listed in the PMRA final decision document revealed a coherent body of evidence indicating that glyphosate-based herbicides could be toxic below the regulatory lowest observed adverse effect level for chronic toxic effects. It includes teratogenic, tumorigenic and hepatorenal effects.

Some effects were detected in the range of the recommended acceptable daily intake (ADI) of 0.3 mg/kg bw/d (which is the same as the one used by the PMRA). The literature review indicated that toxic effects of commercial formulations can also be explained by glyphosate-based herbicides adjuvants, which have their own toxicity, but also enhance glyphosate toxicity. These challenge the assumption of the safety of glyphosate-based herbicides at the levels at which they can be found in food and the environment, although these levels may fall below regulatory thresholds. The authors of the review state:

> *"Neurodevelopmental, reproductive, and transgenerational effects must be revisited, since a growing body of knowledge suggests the predominance of endocrine disrupting mechanisms caused by environmentally relevant levels of exposure."*

- Hepatorenal

Three studies not included in the PMRA final decision document reported hepatorenal changes below the ADI of 0.3 mg/kg bw/d (which is the same used by the PMRA) at levels relevant for environmental exposures (Larsen et al. 2014).

- Hepatotoxic

One study listed in the PMRA final decision document suggested irreversible damage in hepatocytes below 5 mg/kg bw/d (Benedetti et al. 2004). In this study, *"glyphosate administered to rats at a concentration of 4.87 mg/ kg bw glyphosate every 2 days over 75 days induced hepatic leakage of ALAT and*

ASAT, suggesting irreversible damage in hepatocytes." Yet, the NOAEL used by the PMRA for all populations and durations – which is the lowest NOAEL used by the PMRA - is 32/34 (male / female) mg/kg bw/day. It is concerning to see that the lowest NOAEL used by the PMRA is more than 6 times the concentration at which hepatotoxicity has been reported.

- Reprotoxic

Studies listed in the PMRA final decision document report reprotoxic effects below the lowest NOAEL used by the PMRA. One study reported puberty delay and alteration of the functions and structure of testes from 5 mg/kg bw/d (Romano et al. 2010). In other peer-reviewed studies that have exposed rats *in utero*, Roundup altered spermatogenesis from 6 mg/kg bw/d and disrupted serum testosterone levels in the adults (Dalegrave et al. 2007). Another study (Romano et al. 2012) found that maternal exposure to glyphosate-based herbicides (50 mg/kg bw/d) disturbed the masculinization process and promoted behavioral changes, as well as histological and endocrine problems, with consequences to the reproductive parameters of the progeny. It is concerning to see that the lowest NOAEL used by the PMRA is many times higher than the concentration at which reprotoxicity has been reported.

- Teratogenic

Studies listed in the PMRA final decision document report teratogenic effects below the NOAEL used by the PMRA. *"Visceral and skeletal malformations arose from 20 mg/kg bw/d in regulatory studies"* (Antoniou, 2012).

> *"Evidence of teratogenicity was found in the German authorities' draft assessment report on the industry studies that underlie the authorization of glyphosate in the EU (Antoniou, 2012). The lowest dose of glyphosate alone producing an effect led to the decrease in the mean litter size from 7.7 mg/kg bw/ d in a two-generation rat reproductive study (German Federal Agency CPFS, 1998). This was not found in the F2 generation. In a second developmental study, a statistically significantly increased number of fetuses with a dilated heart was found at the lowest dose of 20 mg/kg bw/d, while no fetus was affected in the control group"* (German Federal Agency CPFS, 1998).

Again, it is concerning to see that the lowest NOAEL used by the PMRA is many times higher than the concentration at which reprotoxicity has been reported.

4. Chelation effects on nutrient and toxicant levels in soils and foods

Glyphosates bind (chelates) with vital minerals in soils and plants. Depending on various scientific perspectives, this could lead to depletion of essential minerals, and/or mobilization of less soluble toxic heavy metals. Thus, crops treated with glyphosate may contain higher levels of the neurotoxic carcinogen cadmium (Barański et al. 2014). Cadmium (Cd) is hyperaccumulated in grains, and although Canada has no standard for cadmium in grain, this is monitored by the Grain Commission for compliance with international standards. Excessively contaminated Canadian wheat has previously been sent back from Europe. High Cd levels in Canadian potash used in fertilizers exacerbate this problem that originates in naturally high Cd levels in prairie soils. We acknowledge that this is an active scientific debate, and not all studies point to the same chelation conclusions; nevertheless, the PMRA Decision stipulates that ramifications of chelation are beyond the scope of pesticide assessment, in spite of the chemical having been patented for this capability. The PMRA should conduct a stronger re-evaluation that, at the very least, considers this growing body of literature in its Decision.

B. RISK MITIGATION

1. Riparian buffer strips (RBS) and buffer zones are inefficient as risk management strategies, considering efficacy, environmental persistence, and risks of groundwater and surface water contamination from glyphosate

In the Proposed and Final decisions on glyphosate registration, the PMRA states:

> *"Glyphosate formulations pose a negligible risk to freshwater fish and amphibians, but may pose a risk to freshwater algae, freshwater plants, marine/estuarine invertebrates and marine fish if exposed to high*

> *enough concentrations. Hazard statements and mitigation measures (spray buffer zones) are required on product labels to protect aquatic organisms." (p.13, PMRA, 2015)*
>
> *"The environmental assessment concluded that spray buffer zones are necessary to mitigate potential risks to non-target species (for example, vegetation near treated areas, aquatic invertebrates and fish) from spray drift. " (p.6, PMRA, 2017)*
>
> *"In the terrestrial environment the only risk identified was for terrestrial plants, therefore, spray buffer zones are required to reduce exposure to sensitive terrestrial plants." (p.6, PMRA, 2017)*

These statements implicitly assume both that there is a potential risk posed to non-target species and that no-spray buffer zones are an effective mitigation strategy. However, PMRA fails to provide scientific evidence supporting the efficiency of buffer zones in mitigating glyphosate leaching to aquatic ecosystems. In fact, PMRA's 2005 agricultural buffer zone document explicitly states that it only considers spray drift and not post application runoff and leaching (Pest Management Regulatory Agency, 2005).

Few authors have studied glyphosate runoff through riparian buffer strips (RBS). One of the few studies conducted on the topic, Lin et al. (2011) observed a 60–71% reduction in glyphosate leaching through 4–8 m wide RBS composed of *Festuca arundinacea*, *Festuca* and *Panicum virgatum*, and native *Tripsacum dactyloides* plants. These scientists relied on a homogeneously distributed runoff simulation (using a rotating boom), which makes the result of this experiment unlikely similar to natural heterogeneous settings that occur in the fields. Their study suggests that larger RBS may be effective than narrower ones in trapping sediment bound glyphosate.

In another study, Syversen and Bechmann (2004) concluded that glyphosate-removal is relatively low in terms of efficiency across the RBS (mean: 39%; range approximately from 10-75%). Soluble glyphosate removal efficiency (measured on centrifuged samples) is relatively low (mean 42%;

range 24-70%) and these authors indicate that further investigation of the poorly documented potential of the RBS is warranted. Importantly, according to these authors, RBS removal efficiency for glyphosate may be lower compared to other pesticides.

Syversen and Bechmann (2004) analyzed glyphosate retention in 5 m wide Norwegian RBS composed of various grasses (*Circium arvense* (L.) Scop., *Elytrigia repens repens* (L.) Desv. Ex Nevski, *Phleum pratense pratense* (L.), *Deschàpsia cespitòsa cespitòsa* (L.) Beauv, *Festuca pratensis* Huds.). They relied on surrogate runoff in short-term experiments (5h), and a homogeneous runoff distribution system (perforated gutter). Such settings are hardly representative of heterogeneous natural precipitations and the heterogeneity of natural runoff in a field (Hénault-Ethier, 2017b). Glyphosate was added to a soil and water mixture with total concentrations representing 12-23 µg/g soil. If the glyphosate concentrations used (equivalent to 12 000 – 23 000 µg/Kg of soil in the aqueous mixture in Syversen and Bechmann (2004)) are compared to the soil glyphosate concentrations measured in Québec soils, there is a two order of magnitude difference (mean : 210 µg/Kg, range: 0-317 µg/Kg; Hénault-Ethier, et al. 2017a). Not only are the glyphosate reduction observations of Syversen and Bechmann (2004) study inconsistent with those observed in Québec (Hénault-Ethier, et al. 2017a), the methodology used also strongly reduces the applicability of the results to real life conditions in Canadian fields, and may thus invalidate the conclusions of the study.

In an earlier study, Syversen (2003) suggested high glyphosate (74%) and AMPA (78%) retention efficiency, under natural precipitation conditions in Norway. However, controls consisted of reference plots which were parallel to treatment plots with a RBS (as opposed to measuring before and after on a single RBS), and the authors noted a difference in runoff between the treatment and control plots. This experimental design has several limitations (Hénault-Ethier, 2016; Hénault-Ethier, 2017b). Hence, their conclusions may not be generalizable.

On the other hand, the most recent Canadian scientific findings suggest that vegetated buffer strips have only a very low or weak potential efficiency to minimize glyphosate and AMPA leaching via runoff (Hénault-Ethier, et al. 2017a). Although RBS studies on nutrients commonly suggest that wider RBS have higher removal efficiency, the narrow RBS width promoted by the Quebec provincial government could explain their limited efficacy. However, several

other factors could also be involved. Among these, high phosphorous loads from fertilization may compete for adsorption sites on soils and induce leaching of glyphosate after fertilization, which may be independent of the width of the RBS.

This new research also shows that measuring soil glyphosate concentration before and after a RBS is not sufficient to determine the efficacy of buffer zones to intercept dissolved glyphosate (Hénault-Ethier, et al. 2017a). If RBS are inefficient at intercepting dissolved glyphosate, studies demonstrating the efficiency of RBS at intercepting unfiltered runoff (i.e. Syversen & Bechman, 2003) or particle bound glyphosate (i.e. Lin et al. 2011) may overestimate the potential efficiency to minimize glyphosate transport. This relationship is revealed through the correlation of an increasing pesticide removal efficiency with an increasing particle concentration in runoff (Syversen & Bechman, 2003).

In its final decision, PMRA further states that:

> *"Runoff events can be difficult to predict and the presence of glyphosate in water as a result of runoff or spray drift is expected. Proper application timing and runoff/spray drift mitigation measures can reduce potential impacts." (p.49, PMRA, 2017)*

No scientific evidence is provided by the PMRA to support the runoff/spray drift mitigation measures to reduce potential impacts. The above statement appears contrary to novel evidence:

> *"3-m-wide RBS, even with the use of fast growing willows as efficient phytoremediation agents instead of spontaneous herbaceous vegetation, do not significantly decrease aqueous glyphosate and AMPA leaching in runoff waters." (p.8, Hénault-Ethier et al. 2017a).*

The low intrinsic efficiency of RBS may not be the only limitation of buffer zones as a risk mitigation measure. RBS adoption rates by farmers should also be considered by the PMRA in its final decision. The PMRA states:

> *"Over the last two decades, Canadian growers have adopted best management practices on their farms (such as hedgerow, riparian strip, grass farm road, implementation of no till techniques leaving more plant biomass on the ground for runoff interception as well as the use of buffer zones) to avoid soil, fertilizer and pesticide losses from fields." (p.49, PMRA 2017).*

Though these recommended practices are being increasingly adopted, they are by no means ubiquitous in farming regions. Non-compliance for buffer zone implementation in riparian areas is heavily documented in Canada (see Dagenais 2016 and references therein including Sager (2004)). Only 53% of Québec municipalities require riparian buffer strips in their regulations, and some others require a permit to cultivate in the riparian zone. This is contrary to the *Politique de protection des rives, du littoral et des plaines inondables* of Québec, which recommends variable minimal RBS widths depending on the context.

Prescribed RBS widths are not often accepted by farmers (Dagenais, 2016), because they feel frustrated by the negative impacts, including economic impacts, of establishing and maintaining RBS, and therefore may not adopt RBS recommendations or maintain them (Belzile et al. 2013). Belzile et al. (2013) study suggests that farmers who implement RBS may even be negatively stigmatized by their peers for favoring riparian plant growth. The PMRA does not consider this evidence and the barriers to farmer compliance in its risk mitigation strategy.

The PMRA also failed to consider scientific evidence concerning glyphosate's potential to leach into groundwaters. The PMRA states that:

> *"Monitoring studies conducted throughout Canada indicate that glyphosate is rarely detected in groundwater. Although glyphosate is often detected in surface water, the concentrations detected are at relatively low levels that do not pose a risk of concern." (p.49, PMRA 2017)*

However, a new scientific study conducted in Québec suggests that RBS, which are designed to control runoff, may increase glyphosate infiltration in groundwater (Hénault-Ethier, et al. 2017a). This new study in Quebec echos

similar concerns expressed by others (Krutz et al. 2005).

> *''Potential glyphosate drainage and groundwater contamination potential is theoretically considered low (Cerdeira and Duke, 2006; Gustafson, 1989; Horth and Blackmore, 2009; Scribner et al., 2007) because of potential glyphosate sorption on soil particles (Vereecken, 2005; Wauchope et al., 2002). Despite this fact, high water solubility (12.0 g·L−1; pH 4.3, 25 °C) (EPA, 2009b) may permit glyphosate infiltration under conditions of high precipitation, and especially in the presence of preferential flowpaths, such as macropores (Kjaer, 2005; Vereecken, 2005).'' (p.7 Hénault-Ethier, et*
>
> *al. 2017a)*

Evidence suggests that once in groundwater, glyphosate may become persistent, and this is not considered by the PMRA in its Decision which describes it as ''non-persistent to moderately persistent''.

> *"Common conditions in riparian interstitial or groundwater such as darkness (Mercurio et al., 2014), anaerobic conditions (EPA, 2009b), cold (Helander et al., 2012) and salty environments (Yang et al., 2013), may increase glyphosate persistence." (p.8 Hénault-Ethier, et al. 2017a)*

Hence, in the long term, it is likely that glyphosate contamination would accumulate. The rare detections of glyphosate in Canadian groundwater may be due to low sampling size; glyphosate is known to be present in groundwaters in Europe.

> *"Horth and Blackmore (2009) reported glyphosate detection in 1.7% of 28,000 groundwater samples from 8000 sites between 1993 and 2008 in Europe (>0.1 µg·L^{-1} in 0.9% of the samples)." (p.8 Hénault-Ethier, et al. 2017a)*

New Canadian (Québec) based evidence suggests that glyphosate applied in June persists at least until the following spring in soils and runoff waters and

concentrations of glyphosate equal to those measured during leaching soon after field spraying may be measured the following spring, after sowing and fertilization (Hénault-Ethier, et al. 2017a). This directly contradicts the PMRA (2017) observation that glyphosate is ‘’not expected to carry over to the next year’’ (p.48). This new Canadian evidence needs to be considered by the PMRA (2017), which dismissed similar persistence conclusions from American studies (Battaglin et al. 2014), on the basis that Canada has different ecoregions, climate and soils than the US.

Scientific evidence demonstrates an increasing trend in the frequency in which glyphosate is detected in surface waters of rivers monitored in Québec’s agricultural regions (Giroux, 2015; Giroux and Pelletier, 2012), but this evidence is not considered by the PMRA. New scientific literature reviews suggest that:

> *“Biodiversity and productivity of aquatic communities may be impacted by glyphosate … not only at concentrations below the Canadian chronic aquatic toxicity criteria which was recently augmented to 800 µg·L^{-1} by the Canadian Council of Ministers of the Environment (CCME (Canadian Council of Ministers of the Environment), 2012) but also below the 65 µg·L−1 threshold currently in effect in Quebec (Giroux, 2015).” (Hénault-Ethier, et al. 2017a)*

A Canadian study by Smedbol et al. (2013) was not considered in the Final decision, and demonstrated changes in phytoplankton assemblages at 5 µg·L^{-1} in surface waters. Furthermore, another study demonstrating that antioxidant enzymes (catalase, ascorbate, peroxidase, superoxide dismutase) increase after 24h at ≥ 300 µg/L, by Chesney et al. (2015) was not taken into account in the Decision.

Concerning recommendations specific to formulations and their effects on the environment, the PMRA concludes that:

> *“Certain glyphosate formulations include a surfactant composed of POEA compounds. At high enough concentrations, POEA is toxic to aquatic organisms but is not expected to remain in the environment. While, in general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine*

> *organisms than formulations that do not contain POEA, they do not pose risks of concern to the environment when used as directed on the label." (p.49)*

However, the no-spray buffer zones required by the PMRA for other glyphosate formulations is not increased in presence of the POEA co-formulants. The risk mitigation strategy required by the PMRA for formulations containing POEA thus appears inconsistent with the fact that in general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine organisms than formulations that do not contain POEA.

Indeed, the required buffer zones for the protection of aquatic habitats is one meter for agricultural crop systems and ground boom application methods, as well as in forest systems and non-crop systems. The Buffer Zone is increased to 15, 20 or 25 meters for aerial or airblast applications in agricultural crop, pasture and turfgrass systems. Only in rights of way areas of non-crop land and industrial uses are the Buffer Zones increased to 60 or 100 m. For formulations containing the co-formulant POEA, the required buffer zone to protect aquatic habitats is not increased sufficiently.

According to the PMRA's own guiding principles in the design of agricultural buffers, ''the more toxic the pesticide to a sensitive organism, the larger the buffer zone'' should be (Pest Management Regulatory Agency, 2005). This document appears outdated as it still considers toxicity of the pesticide to a non-target organism to be primarily due to its active ingredients (some formulations are now known to be more toxic than active ingredients) and requires a dose-response relationship between active ingredient pesticide concentration (which is not the case for endocrine disruptors). Furthermore, this guideline document correctly states that ''Off-site spray drift and deposition are largely independent of the physical/chemical characteristics of an active ingredient, but may be dependent on the physical/chemical characteristics of a formulation;'' However, PMRA recognizes that it does not have the proper information to correctly assess spray drift potential of formulations (''however, no information is provided to the PMRA on the drift reducing capabilities of the formulation ingredients in the pesticide product.'') (p.13).

Concerning the width of buffer zones, the recommended widths proposed by PMRA appear insufficient, as 3 m RBS were inefficient to mitigate glyphosate

leaching to surface waters (Hénault-Ethier et al., 2017a).

Weed field communities are voluntarily impacted by herbicides, but plants may involuntarily be impacted with the occasional drift to non-target habitats (Gomes et al., 2014) which may reach 10% of the sprayed volumes (see Jobin et al., 1997, and references therein). Herbicide spray drifts are generally considered negligible beyond 10-15 m in opened areas (no vegetation) under light to moderate winds (compiled by Gove et al., 2007), but may reach as far as 30 m in forested areas abutting fields (Elliot, 1983). Agricultural habitats are known to be impacted by herbicides in Canada, an impact that influences the species composition of fields and contiguous areas (Jobin et al, 1997). This impact has been evidenced on transects as short as 10 m, crossing midway the field and the uncultivated zones. The various herbicides included in these studies (i.e. atrazine, metolachlor, dicamba and glyphosate) were responsible for a reduction in Shannon diversity (a diversity measurement index). The conclusions described herein are echoed by recommendations in the monarch section (A.1) of the current NOO.

2. Efficacy of labelling as a risk management strategy: Knowledge gap not acknowledged by the PMRA

In the PMRA's Decision, it is stated that "the PMRA is granting continued registration of products containing glyphosate with requirements of additional label updates to further protect human health and the environment.'' The PMRA does not provide *any* scientific grounds to defend that labelling is an effective risk management strategy in the protection of human health and the environment from unacceptable risks.

The PMRA should, at the very least, acknowledge that there is a significant knowledge gap as it concerns the efficacy of labelling as a risk management strategy. The PMRA should also acknowledge that the limited research that does exist indicates that, in other contexts, precautionary statements on labels are often not interpreted correctly by users (Rother 2008). For many users, the very fact that a product is marketed is seen as evidence of its safety, and labels are viewed as information overload. Further, illiteracy, poverty and a perception that exposure to pesticides is an inevitable part of a farm workers work results in limited adoption of safety precautions while using and storing pesticides (Kiriaki

et. al, 2014).

Relying on labelling as a risk mitigation strategy puts the onus on individuals and leaves important gaps in the protection of Canadians' health and environment. This strategy should not be relied upon until a robust, independent evaluation of the effectiveness of precautionary label statements be conducted within the Canadian context, and must include migrant agricultural labourers as part of the sample, considering significant language and cultural barriers. This study is needed in order to understand if those applying pesticides in Canada read and understand precautionary label statements, and if the vast majority of them ultimately follow the instructions on the label intended to reduce risks. Until then, the PMRA must acknowledge the knowledge gap in the efficacy of of labelling as a risk management strategy, and this must be clearly stated in the Decision so that Canadians know that this risk management strategy is not based on scientific grounds.

C. Methodology

Upon review and through the process of completing this Notice of Objective, the methodology employed by the PMRA to conduct a re-evaluation appears flawed.

1. **The need for systematic review methodology and concerns with conflict of interest**

In an era where conflicts of interests are said to bias the regulation of pesticides (United Nations, 2017), the government needs to be increasingly transparent and systematic in the evaluation of products which bear inherent risks (i.e. pesticides are by definition lethal, and risk must be managed accordingly).

Systematic Review (SR) was formalized originally to consolidate scientific evidence regarding clinical interventions, and in the US the Agency for Health Research Quality has detailed protocols for SR, to develop evidence for their program. Internationally the Cochrane Collaboration is a leader for clinical SR, and Oxford University has some helpful resources. The methodology is slightly more recent for environmental health, albeit now mature. The US National Toxicology Program undertook an extensive, collaborative process to develop methodology, that was published along with a small series of examples, in Environmental Health Perspectives (Rooney, Boyles et al. 2014).

In July 2017, the methodology was further detailed, and applied to endocrine active chemicals, in a large project published in the US by The National

Academies of Sciences Engineering and Medicine (2017).

In fact, there exist several excellent publications to standardise methodology used in reviewing toxicological effects that have been developed for the evaluation of various substances or in different contexts (Rooney et al 2016; Haute autorité de santé (HAS) 2013; Office of Health Assessment and Translation (OHAT) 2015; EFSA 2017; NAS 2017).

Rather than relying upon others' assessments, the PMRA should be relying upon primary data. Systematic search on pesticide toxic effects needs to be conducted in a systematic way to avoid bias. Commonly, key words used are listed. Based on the studies found in databases, some may be excluded or included after reviewing their abstract. The criteria for doing this need to be presented. To ensure transparent reporting, a PRISMA type diagram should be used. "The flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions." (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx). The data within each study retained should be detailed in a tabulated form (for example stipulating the population studied, exposure, comparators, outcomes and results). Finally, a meta-analysis may when appropriate be used to better understand potentially generalisable conclusions from individual studies. Finally, each study should be graded systematically to identify strengths and weaknesses, potential conflicts of interests, and funding sources, and sensitivity analyses should be carried out on these bases. This would help to identify things like whether a trend in conclusions correlates with funding sources. An example of a strong table format is provided in the Table 2.

When Health Canada indicates that it carries out weight of evidence analyses, this needs to be substantiated by transparently presenting the methods used to weigh evidence.

Table 2: Example of information that could be compiled by PMRA in the evaluation of the quality of the evidence health outcome of pesticide exposure. Extracted from (Rooney et al. 2016)

Table 9. Evidence Profile Table Format										
Example of the type of information that will be in an evidence profile for immune health outcomes										
Body of Evidence	**Risk of Bias**	**Unexplained Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Magnitude**	**Dose Response**	**Residual Confounding**	**Consistency Across Species/ Model**	**FINAL RATING**
Evidence stream (human or animal)	Serious or not serious	Serious or not serious	Serious or not serious	Serious or not serious	Detected or undetected	Large or not large	Yes or no	Yes or no	Yes or no	**Final Rating**
(# Studies) Initial Rating	• Describe trend • Describe key questions • Describe issues	• Describe results in terms of consistency • Explain apparent inconsistency (if it can be explained)	• Discuss use of upstream indicators or populations with less relevance	• Discuss ability to distinguish treatment from control • Describe confidence intervals	• Discuss factors that might indicate publication bias (e.g., funding, lag)	• Describe magnitude of response	• Outline evidence for or against dose response	• Address whether there is evidence that confounding would bias toward null	• Describe cross-species, model, or population consistency	**High, Moderate, or Low**

2. Duplicates and methodological rigour

There are inevitably duplicate reports in initial stages of information gathering, but following systematic review of a body of science there should be no obvious duplicates remaining. This would be an indication of sloppiness, lapses of systematic reviewing methods and perhaps deficiencies in electronic database maintenance and support. Without searching for duplicates, there are many immediately obvious in the sources referred by the PMRA for reading room review. For instance, 4 sets in PRVD2015 were identified with a quick search:

- 2460763 and 1142753 (1996, Aerobic metabolism of [14C] glyphosate in sandy loam and silt loam soils with biometer flask. PTRL Report ND. 1301. PTRL Study No. 368. R.D. No. 1031. DACO: 12.5, 8.2.3.1, 8.2.3.4.2);
- 1235214 and 1235215 (1990, Chronic study of glyphosate administered in feed to albino rats, DACO: 4.4.1, 4.4.2);
- 1161786 and 1161795 (1993, Glyphosate 104 week dietary carcinogenicity study in mice, DACO: 4.4.1,4.4.2)
- 1184837 and 1184838 (1981. A lifetime feeding study of glyphosate (roudup technical) in rats, DACO: 4.4.1, 4.4.2)

These studies may be single studies repeated, or different parts of one study divided into separate references without clear labelling. Either way, this is poor practice because it gives the illusion that there is more evidence than there actually is and may facilitate “double-counted” findings carrying more weight than they should.

Appendix 1

The PMRA used the following publically available data in their re-evaluation decision on glyphosate to evaluate the impact of glyphosate on milkweed and monarchs. Below are a summary of some of the key findings of the studies, which either limited in terms of milkweed and monarch data and/or present conclusions that have not guided the PMRA's re-evaluation Decision.

2469290 Boutin, C., Elmegaard, N., Kjaer, C., 2004, toxicity testing of fifteen non-crop plant species with six herbicides in a greenhouse experiment: implications for risk assessment - Ecotoxicology, Volume 13, Pages 349 to 369, DACO: 9.8.4

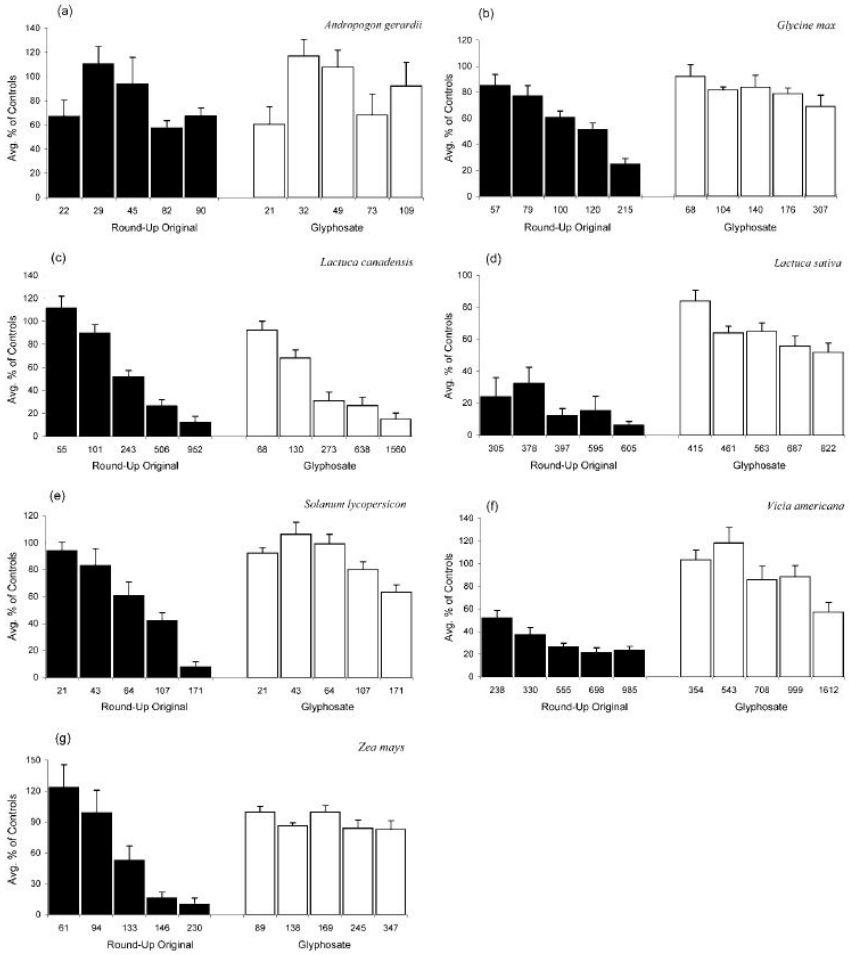
- Not mentioned in NOO 2017/06/26
- Greenhouse experiment on 15 non-crop plants sprayed with 6 herbicides
  - **Glyphosate toxicity on *Asclepias* sp. not assessed, though toxicity on several melliferous flowers (i.e. *Solidago Canadensis*) were assessed.**
- Plants used in Danish/Canadian data set were nearly always more sensitive to glyphosate than in the US EPA assessments.
  - Relying on ''US EPA data would have underestimated the risk of adverse effects for several species of the Danish/Canadian database: all 15 species for glyphosate (…)''
- Roundup Bio 360 g/l with 480 g glyphosate isopropylamin-salt, Monsanto
  - 1440 g ai/ha applied at 4-8 leaf stage
  - 41% active ingredient and 59% of other unspecified ingredients
- Different sensitivities between US and Canadian/Danish studies may have to do with the inert (non-herbicidal) ingredients which affect spreading of spray droplets upon contact with foliage, and absorption within the plant.
- "Glyphosate is also more toxic to hard-to-kill perennial species in the fall than in the spring when plants are fully grown thus have a large contact surface for penetration of the herbicide that can be translocated into the storage organs" (Dekker and Chandler, 1985).
- "Glyphosate has been shown to affect seed germination when parent plants were sprayed during the seed development (Blackburn and Boutin, 2003)."
- Conclusion

- ‘’It is very likely that the current suite of species prescribed in current guidelines will not be adequate for the protection of habitats, e.g., field margin species, in agricultural areas. The nonrandomness in the current selection of species favoured in the US EPA and other countries (Holst and Ellwanger, 1982; Organisation for Economic Co-operation and Development, 1984) causes an unacceptable bias with consequences that risk is underestimated. Some basic rules should be followed in the selection of plants: (1) No crop species on which products will be applied, (2) No known species for which the product is presumably not toxic, often revealed by efficacy data (see Boutin and Rogers, 2000; Boutin et al., 1995), (3) Mostly non-crop species and preferably species of field margins. Many non-crop species are easy to grow in greenhouses. Factors that could be considered in the selection of non-crop species to be tested are seed size, growth rate and requirements for germination. In this comparative analysis, however, it was not possible to distinguish between effects caused by the plant species selected and effects induced by the formulation of the herbicides tested, and this alone commands further research.’’
- Based on the author’s conclusion, it appears that *Asclepias* sp. could be a good candidate for non-target plant toxicity testing.
    - **We recommend further testing on glyphosate toxicity on milkweed as part of the non-target plant toxicity assessment in Canada.**

2482641 White, A.L. and Boutin , C., 2007, Herbicidal effects of non-target vegetation: Investigating the limitation of current pesticide registration guidelines - Environmental toxicology and Chemistry, Volume 26, Number 12, Pages 2634 to 2643, DACO: 9.9

- Not mentioned in NOO 2017/06/26
- ‘’Current pesticide registration guidelines may be inadequate at predicting the effects of herbicides on wild plants and habitats.’’
- ‘’ Results showed that current regulatory protocol will likely underestimate herbicide phytotoxicity if testing does not include data for the complete tank-mix formulation.’’
- ‘’Depending on the cultivar included in a risk assessment, conclusions regarding the phytotoxicity of any given herbicide may differ.’’

- ‘’Pesticide regulatory guidelines would be improved if wild species were included in testing.’’
- Protocol
    - ‘’All species were exposed to a one-time herbicide application at the two- to six-leaf stage.’’
    - ‘’Round-Up Original (Monsanto Canada, Mississauga, ON) containing 356 g ai/L glyphosate was applied.’’
- ‘’In the case of radish (*Raphanus sativus*), no close native relatives could be found to meet all the selection criteria, so milkweed (*Asclepias syriaca*) was selected since this species has similar morphology, is commonly found in field margin habitats, and is of ecological relevance.’’
    - Not all species were included in every experiment (A, B and C experiments)
        - No testing everything on *Asclepias* sp.
            - Not for : A use in the formulated product compared to active ingredient study;
            - Not for B: use in the cultivar variability experiment;
            - Yes for C : use in the crop
            - and noncrop herbicide sensitivity comparison test.
- ‘’ Current pesticide registration guidelines in Canada and the United States require the use of 10 different crop species meeting certain criteria.’’
    - ‘’For all species for which it could be calculated, the IC25 was much lower for the formulated product than it was for the active ingredient alone, indicating that glyphosate is much less toxic to the species tested than the formulated product Round-Up Original.’’
    - ‘’glyphosate elicited a significantly less toxic response than Round-Up Original’’
        - Not tested on *Asclepias sp.*
- Figure 1: Comparison of the effect of the formulated product Round-Up Original and its active ingredient glyphosate on biomass (expressed as a percent of the controls) for seven different terrestrial plant species. Herbicide doses are shown as grams of active ingredient applied per hectare (g ai/ha).



- See Table 2 of original study.
- ‘’ the way in which dose-affected biomass differed between Round-Up Original and glyphosate for some plant species.’’ (i.e. there is interaction)
- ‘’Past research regarding the toxicity of different glyphosate formulations reported that additives, such as surfactants and adjuvants, are quite effective at increasing the phytotoxicity of active ingredients [19–21] and can result in differences in toxicity between formulations [22]. The present study differed from previous studies in that any increased toxicity due to nonformulation additives was controlled for by adding the surfactant Agral-90 in a rate recommended on the label of Round-Up Original to both the active ingredient and the formulated product. Thus, the present study included two treatments: the complete tank-mix formulation (active ingredient unknown inert ingredients prespray surfactant) that would actually be sprayed in an agricultural field in an attempt to control weeds and the most

likely chemical combination submitted for risk assessment by registrants for regulatory purposes (active ingredient surfactant).''

- ''The study was simply designed to determine if the tank-mix formulation of Round-Up Original is more toxic than the combination of active ingredient plus surfactant. Any variation in phytotoxicity between the two chemical treatments is likely due to the unknown ingredients, generally thought to be inert, contained in the formulated product.''
- "Although it is changing [5,7], regulatory agencies generally request testing only with the active ingredient, and therefore the estimated herbicide phytotoxicity would likely be even lower since the surfactant may not have been included. **How additives will affect herbicide efficacy can be difficult to predict and quite variable [22], and many more active ingredients must be compared to their formulated products before broad conclusions can be made.** Nonetheless, the results gathered in the present study, together with previous research [15,16,19– 22], strongly suggest that **pesticide registration guidelines should expand to consider the toxicity of the formulated products, along with any surfactants or adjuvants that may be added if these chemicals are listed on the herbicide label.** Since active ingredients are not used alone and neither are the additives, **toxicity data should consider the possible synergistic effects of these chemicals and expand to require data for the tank mix of formulated products; otherwise, their toxicity may be greatly underestimated**."

2482642 J.B. Wyrill, III and O.C. Burnside, 1977, Glyphosate toxicity to Common Milkweed and Hemp Dogbane as influenced by Surfactants - Weed Science, Volume 25, Number 3, Pages 275 to 287, DACO: 9.9

- Not mentioned in NOO 2017/06/26
- '' Common milkweed can be effectively controlled with glyphosate; whereas, hemp dogbane has exhibited some tolerance to glyphosate. Differential response has been attributed to less glyphosate absorption by hemp dogbane as compared to common milkweed.''
- Protocol
  - Greenhouse experiments
  - isopropyl-amine salt
  - Surfactants were included in the spray solution as percentage (w/v) active surfactant

        - ‘’Common milkweed and hemp dogbane seedlings were sprayed with glyphosate at 0, 0.28, 0.56, and 1.12 kg/ha alone and in combination with 22 surfactants at a concentration of 1% (w/v)’’
        - ‘’Nine surfactants from the initial study were selected and tested alone (1% w/v) and in all possible dual combinations (0.5% of each surfactant) with glyphosate at 0.07 and 0.28 kg/h’’
        - ‘’Effects of surfactant alone were minor on both common milkweed and hemp dogbane compared to the effects of glyphosate in combination with surfactants’’
    - Results
        - ‘’All surfactants tested except Darvan No. 1 either increased or had no effect on glyphosate phytotoxicity. Darvan No. 1 was less effective on common milkweed than glyphosate without surfactant’’
        - ‘’Cationic surfactants were more effective in enhancing glyphosate phytotoxicity than other ionic forms. Anionic and zwitterionic surfactants were generally less effective than non- ionic surfactants’’
        - ‘’Collectively, the data show the amine containing surfactants to be the most effective with effectiveness increasing with increases in HLB and degree of ethoxylation. Cationic surfactants were generally more effective than the nonionic surfactants.’’
        - ‘’ Common milkweed and hemp dogbane are known to have quite different cuticle structure, yet both species responded similarly to a wide range of surfactants. If surfactants exerted a major influence on glyphosate movement through the cuticle, greater differences might be expected between these species’’
            - ‘’ Thus, the primary effect of the surfactant is probably not on the cuticle. It is more likely that the main effect of the surfactant is on the plasmalemma, since it has been shown that surfactants affect permeability of this membrane’’
        - ‘’ When a surfactant-glyphosate drop is placed on the leaf surface, evaporation may tend to shift the equilibrium from glyphosate in solution to glyphosate associated with the surfactant micelle. Thus more glyphosate might be associated with the surfactant under these conditions’’

        - ‘’The plasmalemma is thought to be composed of two layers of protein suspended by a bimolecular layer of lipid (21) and would constitute a barrier to penetration by a molecule such as glyphosate.’’
    - Conclusion
        - “It appears that surfactant effectiveness is dependent to some extent on surfactant HLB, chemical type, and possibly molecular size. An effective **surfactant** is a critical component of any glyphosate spray mixture and **could conceivably reduce the glyphosate rate requirement for the control of common milkweed** and increase the susceptibility of hemp dogbane to glyphosate.”
        - **Based on this study, we argue that PMRA should call in studies on the effect of a wide range of commercially available glyphosate based herbicides on milkweeds**.

2203560 United States Environmental Protection Agency, 1993, Reregistration Eligibility Decision (RED) Glyphosate, DACO: 12.5

- Not mentioned in NOO 2017/06/26
- P.11/291

EPA does not expect that most endangered terrestrial or aquatic organisms will be affected by the registered uses of glyphosate. However, many endangered plants as well as the Houston toad (due to its habitat) may be at risk. EPA is deferring any use modifications or labeling amendments until it has published the Endangered Species Protection Plan and has given registrants guidance regarding endangered species precautionary labeling.

- Indirect effect on endangered species (i.e. effect on milkweed affecting monarch butterfly) is not evidenced. Mere citation of:
    - ‘’Based on the toxicity data and the estimated exposure, it is not expected that endangered terrestrial or aquatic organisms will be affected from the use of glyphosate on the registered uses since the EEC's are well below the endangered species criteria (birds= 1/10 LC50, aquatic organisms= 1/20 LC50). However, many endangered plants may be at risk from the use of glyphosate on the registered use patterns.’’
    - Endangered Species Statement
        - ‘’The Agency does have concerns regarding exposure of endangered plant species to glyphosate.’’ (p.95)

- ‘’Because a jeopardy opinion resulted from these consultations, **the agency imposed endangered species labeling requirements in the Registration Standard to mitigate the risk to endangered species.** Since that time, additional plant species have been added to the list of endangered species. At the present time, EPA is working with the FWS and other federal and state agencies to develop a program to avoid jeopardizing the continued existence of all listed species by the use of pesticides. When the Endangered Species Protection Program is implemented and subsequent guidance is given, endangered species labeling amendments may be required on affected end-use products. Labeling statements for end use products will likely refer users to county specific bulletins specifying detailed limitations on use to protect endangered species.’’ (p.95)
- Effect on non-target insects restricted to honeybee
    - No other mention of insects (in the searcheable terms)
- No mention of monarch (in the searcheable terms)
- No mention of milkweed nor *Asclepias* (in the searcheable terms)

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