Health Canada | Santé Canada

Pest Management Regulatory Agency | Agence de réglementation de la lutte antiparasitaire

JAN 11 2019

Reference No. 2017-3055

Annie Bérubé
Équiterre
75 Albert St. Suite 300
Ottawa, ON
K1P 5E7

Dear Ms. Bérubé,

Re: Notice of Objection to Re-evaluation Decision RVD2017-01, Glyphosate

Your notice of objection, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), regarding the re-evaluation decision for Glyphosate has now been reviewed and assessed in accordance with the PCPA and *Review Panel Regulations*.

The purpose of a notice of objection is to identify the area of science supporting the re-evaluation decision to which objection is taken, to provide the scientific basis of the objection and to request that the area of science in question be referred to a review panel for reconsideration and recommendation.

The PMRA has taken all reasonable measures to ensure impartiality in determining if a panel should be established. The notice of objection, including the scientific rationale, was assessed by a team of PMRA evaluators who were not involved in the original re-evaluation decision. This team provided recommendations as to the requirement for a review panel based on the validity and the scientific plausibility of the issues raised in the notice. The factors to be considered in determining whether to establish a review panel include:

- whether the information in the notice raises scientifically founded doubt as to the validity of the evaluations, on which the decision was based, of the health and environmental risks and the value of the pesticide; and
- whether the advice of a review panel of expert scientists would assist in addressing the subject matter of the objection.

The following information was received and reviewed in support of your notice of objection:

- Notice of Objection Form
- June 26, 2017 and July 24, 2017 Letter to Hon Jane Philpott

The information which you submitted in support of your objection does not meet either of those factors and, accordingly, does not provide a basis for the establishing of a review panel. As a consequence, a review panel will not be established to reconsider the regulatory decision in response to your request.

The issues raised in the notice of objection are attached to this letter are **in bold text**, followed by PMRA responses which are not (see Attachment 1).

Should you have any questions regarding this letter, please contact Charles Smith at 613-736-3625 or charles.smith@canada.ca. Please quote Reference Number 2017-3055 in any correspondence regarding the Notice of Objection to re-evaluation of glyphosate.

Yours truly,

Peter Brander
Chief Registrar
Pest Management Regulatory Agency

c.c.
Louise Henault-Ethier, Chef des projets scientifiques: Fondation David Suzuki

Kim Perrotta, Executive Director: Canadian Association of Physicians for the Environment

Tim Gray, Executive Director: Environmental Defence

Meg Sears, Chair, Prevent Cancer Now

Attachment 1

Comment 1: A comment was received which contained the most recent open letter (May 2017) from Dr. Christopher Portier, Chair of the IARC Committee, to Jean-Claude Juncker, President of the European Commission, concerning the European Food Safety Authority's (EFSA's) re-evaluation of glyphosate. The open letter states that, following an evaluation of the raw tumour data from the EFSA re-evaluation, Dr. Portier believes that the evaluations applied to the glyphosate data are scientifically flawed (specifically as it pertained to statistical analysis), and any decisions derived from these evaluations will fail to protect public health.

PMRA Response:

In June 2017[a], EFSA and the European Chemicals Agency (ECHA) with the support of the Federal Institute for Risk Assessment (Germany; BfR), the lead country performing the re-evaluation, responded to Dr. Portier's open letter (May 2017). As stated in the EFSA/ECHA joint response, statistical analysis provides an important tool in a risk assessment. The response further notes, however, that "the results of any statistical analysis and its related uncertainties have to be weighted for their biological relevance to arrive at a comprehensive toxicological evaluation of the substances at hand."[b]

The signing authorities on the joint response concluded that "Overall EFSA and ECHA are of the opinion that all the findings on the chronic rodent carcinogenicity studies referred to in your letter have been adequately considered and therefore we see no need for our evaluations to be revisited."[c]

The PMRA is in agreement with the EFSA and ECHA conclusion that the statistical elements of the study have been adequately considered. Furthermore, the PMRA conducted an independent assessment of the data during the re-evaluation. Accordingly, the PMRA has determined that the statistical analysis and the PMRA evaluation do not need to be re-assessed.

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[a] EFSA (European Food Safety Authority) and ECHA (European Chemicals Agency). 2017. Re.: Your letter Review of the Carcinogenicity of Glyphosate by ECHA, EFSA and BfR. 06 July 2017. Available online from https://www.efsa.europa.eu/sites/default/files/170706-glyphosate-letter.pdf [Last accessed August 30, 2018]
[b] Ibid
[c] Ibid

Comment 2: In discussing the Portier open letter to Juncker (May 2017), Équiterre, the David Suzuki Foundation, the Canadian Association of Physicians for the Environment, Environmental Defence, and Prevent Cancer Now, cited three studies from the PMRA database. These studies consisted of one genotoxicity study in hamster cells and two chronic rat toxicity studies. This objection noted that findings related to cancer were dismissed by the PMRA due to lack of dose-response in the genotoxicity study and lack of dose-response in the tumour data and use of historical control data in the chronic toxicity studies. The objection states in each case that, "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." In conclusion, the "… dismissal of such evidence is inappropriate based on most modern methodologies and knowledge."

PMRA Response:

The suggestion that endocrine effects can occur in a non-dose-related manner is still being debated in the scientific community. Nonetheless, dose-response remains a relevant consideration in determining whether a change is treatment-related within a weight of evidence context. Additionally, historical control data are an important consideration in determining whether the concurrent controls are behaving as expected along with the incidence of spontaneous lesions in the source populations. When determining whether a lesion is related to treatment, reviewers consider many independent and inter-related factors. In the cases of the tumours and hyperplasia in these two chronic toxicity studies, the weight of evidence included the lack of equivalent tumours in the many other chronic toxicity studies in rats, lack of precursor lesions in the study, the historical control data that indicated that the tumour incidences were within the spontaneous rate of tumours, and the lack of a dose-response.

In summary and as stated in RVD2017-01, the PMRA considered multiple lines of evidence from various toxicity studies in assessing the potential for glyphosate to affect endocrine systems. Studies conducted by the NTP (National Toxicology Program), guideline two-generation reproduction toxicity studies, as well as studies conducted under the US EDSP program (United States Endocrine Disruptor Screening Program), were considered. Glyphosate has not been shown to interact with any specific endocrine pathway and has no physical / chemical properties or structural similarity to other chemicals that are known to interact with the endocrine system. Finally, the US EPA completed a weight-of-evidence assessment on results obtained from the EDSP assays and concluded that glyphosate does not interact with estrogen, androgen, or thyroid pathways and that additional Tier 2 data were not triggered.

Comment 3: A comment was received that they object to the PMRA's "Failure to consider critical evidence associated with glyphosate's impact on microbiomes – for humans and in the soil – as a patented antibiotic." Included in the comment is a table of studies in the glyphosate database considered by the PMRA where the objectors posit that the changes in stool consistency can be correlated with possible effects on the gut microbiota.

PMRA Response:

As stated in RVD2017-01, there is very little scientific evidence to support the claim that glyphosate has any direct impact on human gut microflora, or has any subsequent health effect. Several reports[d,e] postulate that environmental chemicals may potentially lead to changes in normal gut microbiota. However, information to date is based on in vitro studies, with in vivo evidence being very limited and inconclusive. Regarding the eight studies identified by the objectors as having possible effects on the gut microbiota, such effects occurred in the presence of other systemic toxicity. The reference doses established by the PMRA, and documented in PRVD2015-01, are lower than the doses that produced systemic toxicity and are therefore protective of potential effects on the gastrointestinal tract.

Comment 4: A comment was received that the PMRA evaluate the chronic health impacts of co-formulants included in all commercial formulations containing glyphosate registered in Canada. Specifically, the objectors contend that the PMRA is ignoring scientific knowledge of recent years on the genotoxicity of components of commercial formulations other than the active ingredient. Furthermore, the objection took issue with the approach the PMRA took in assessing POEAs, a group of formulants used in some Canadian glyphosate End-Use Products (EPs). Specifically, that the PMRA didn't actually assess the toxicity of POEA and relied on the EPA assessment of ATAE. Also that the PMRA didn't present how it ensures that the EPA had taken into account all data on the subject, the most recent published results or did a credible evaluation.

PMRA Response:

As stated in RVD2017-01, the PMRA considered the studies on genotoxicity of the formulations reported by IARC. Use of these genotoxicity studies in the Canadian hazard assessment was limited by lack of information on the composition of the formulations studied and/or use of model systems that were of limited relevance to the human health risk assessment. In other cases, genotoxic effects were observed at exceedingly high and/or cytotoxic doses. Genotoxic effects occurring at cytotoxic dose levels suggest that those effects are due to toxicity rather than direct DNA-acting properties of glyphosate-formulated products. As stated in PRVD2015-01, in 2010, the US EPA completed a human health risk assessment for phosphate ester, tallowamine, ethoxylated (ATAE), which is a subfamily of the class of compounds known as POEA. Due to the nature of the risk assessment for a group of compounds, the studies were performed on ATAE and related chemicals in order to determine a safe level of 20% in the end-use product.

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[d] Shehata AA, Shrödl W, Aldin AA, Hafez HM, Kürger M. 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Current Microbiology 66(4): 350-358. Available online from http://link.springer.com/article/10.1007%2Fs00284-012-0277-2 [Last accessed September, 2018]

[e] Dietert, RR. The Microbiome in early life: self-completion and microbiota protection as health priorities. Birth Defects Research (Part B) 101: 333-340 (2014). Available online from http://onlinelibrary.wiley.com/doi/10.1002/bdrb.21116/abstract [last accessed September, 2018]

Based on the fact that data were bridged to ATAE and other related compounds to form the conclusion for ATEA in general, it was considered acceptable to bridge the conclusion to other related chemicals, and the US EPA currently uses this assessment as the basis for the approval of POEA compounds. The US EPA assessment is considered to be applicable to the Canadian use pattern and can be relied upon by PMRA to evaluate POEA risks. The EPA report on ATEA provides the criteria used by the EPA to perform the risk assessment on ATAE. This assessment was considered acceptable by the PMRA. Furthermore, the PMRA did have access to the studies on which the EPA assessment was based and these studies were considered as part of PMRA's decision making process.

Comment 5: This objection states that studies referenced in a literature review cited by the PMRA contained adverse findings at doses lower than the LOAELs in the chronic studies and, in some cases, below those of the ADI.

PMRA Response:

The studies cited as part of this comment were conducted on formulations of glyphosate sold in Brazil or Argentina. As these formulations are not on the Canadian market, the studies are not relevant to the Canadian risk assessment.

Comment 6: PMRA staff only considered four peer reviewed sources related to milkweed and monarchs in their decision. These sources are either limited in their conclusion or 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;

PMRA Response

As discussed further below, a large number of studies were reviewed to support the glyphosate risk assessment on non-target plants. Of all the reviewed studies, White and Boutin (2007) included a toxicity endpoint for milkweed specifically, which was incorporated into the original PMRA risk calculations during the re-evaluation. PMRA concurs with the objectors that milkweed was not tested in Boutin et al. (2004). No other toxicity endpoint for milkweed was found during the re-evaluation and none was provided by the objectors.

In addition, in the NoO appendix, objectors questioned not using the Danish /Canadian dataset from Boutin et al. (2004) in the PMRA risk assessment, since results were more sensitive than in other sources. This reference was reviewed in detail by PMRA; however, results were not considered in the glyphosate risk assessment due to study limitations. A close examination of this study revealed that some unforeseen problems with the greenhouse lighting system arose over the course of the trials and plants underwent longer daylight exposure (Boutin et al., 2004, p. 355). Although the extent of the impact on experimental results is unclear, this technical problem may have increased the toxic response. Prolonged exposure to light can induce photoinhibition and photodamage, and by extension, it may intensify the impact of herbicides. It is noted that results reported in this study are very different (show more toxicity) than those reported in a similar study conducted at a later date (Boutin et al., 2010) and for which there were no technical problems. The 2004 study was not included in the assessment as to not introduce a bias that was most likely due to an experimental anomaly rather than actual toxic effects.

While not directly related to milkweed, and outside the scope of the glyphosate re-evaluation, the objectors also pointed out that study conclusions from Boutin et al. (2004) highlight that the current suite of species prescribed in current pesticide test guidelines may not be adequate for the protection of habitats e.g., field margin species in agricultural areas. This question on the number and type of species for toxicity testing and whether or not the recommended surrogate species in current guidelines represent an adequate safeguard for environmental protection has been highly debated. Scientific studies have shown that crops can be used as surrogate species for related wild species (Boutin and Rogers, 2000; Clark et al., 2004; Olszyl et al., 2006; White and Boutin, 2007) and that they can be more or equally sensitive compared to wild species (McKelvey et al., 2002). As an example, radish is one of the required test species cited in current registration guidelines in Canada and United States, and this crop has a similar morphology to milkweed. White and Boutin (2007) paired radish and milkweed due to this similarity in order to compare the sensitivity of crops vs. wild plant species. Furthermore, it is important to note that White and Boutin (2007) and Boutin et al. (2010) did not find significant differences in sensitivity between crops and related wild species, even though they recommend including wild species in regulatory testing regimes. Realistically, it is only feasible to test a small subset of plant species which is then used to represent the hundreds of species that are representative of the terrestrial habitats that are being protected. Given that existing research shows no increased toxicity overall in wild species compared to related crop species, using the results of these toxicity tests for regulatory purposes is believed to be reasonably protective of terrestrial habitats.

Specifically with respect to the toxicity of glyphosate to non-target plants, PMRA went well beyond the current guideline requirements to support the risk assessment on non-target plants. Both unpublished studies (provided by registrants) and studies published in the open scientific literature were reviewed, thereby providing a relatively large amount of information to support the assessment. Overall, data for a total of 50 plant species were considered. This dataset included 29 wild species commonly found in field margins, open habitats and roadsides, such as species from the Asteraceae, Lamiaceae and Polygonaceae families (PRVD 2015-05, Table X.14) which are recognized to be of ecological relevance (Boutin et al, 2004; White and Boutin, 2007). In addition, the studies used in the risk assessment reported measured toxicity endpoints, as opposed to the references cited by the objectors which lack quantitative endpoints. Quantitative endpoints are required by the PMRA to characterize the toxicity and quantify the risk of pesticides for non-target terrestrial plants.

Furthermore, the endpoints for all 50 species including milkweed were included in a Species Sensitivity Distribution (SSD) analysis for plants to calculate a HC_5 (hazard concentration) which protects 95% of the species assemblage. The SSD method is based on the assumption that a subset of species can be used to represent the broader plant community (Aldenberg and Slob, 1993). The resulting HC_5 for glyphosate was used in the risk assessment and was also used to calculate appropriate buffer zones to mitigate the risk to non-target plants found in field margins. The number of species used in the SSD calculations, and by extension used to calculate the buffer zones, was also greater than is typically recommended for SSDs. The minimum number of recommended species varies between sources, ranging from as low as 5 species (Aldenberg and Slob, 1993) to a suggested sample size of 15 to 55 species (Newman et al., 2000). It is noteworthy that the HC_5 obtained from the SSD analysis for glyphosate is more protective (i.e., lower) than the milkweed endpoint reported by White and Boutin (2007). As such, the buffer zones calculated for glyphosate are expected to adequately protect milkweed found on the perimeter of the treatment area.

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

The risk assessment of glyphosate on non-target plants considered not only studies conducted with the glyphosate technical grade active ingredient, but also studies conducted with various formulated end-use products, with and without the surfactant POEA (PRVD2015-01, Table X.13 and X.14; also see the list of references containing information on formulations, below). Based on this information, PMRA concluded that glyphosate formulations could be more toxic to terrestrial plants than the glyphosate technical active ingredient alone (PRVD2015-01, p.32 and Table X.17). As such, the risk assessment did in fact focus on the formulated products, and buffer zones were calculated using endpoints from tests conducted with these products. Note that this issue was already addressed in a response to a similar concern that was received during the re-evaluation consultation period (p.53 of RVD2017-01). The RVD response is similar to the current response.

White and Boutin (2007)	The glyphosate formulation Round-Up Original was tested on a number of wild species including milkweed. This study also included a component which explored the impact of adding a surfactant to the tank mix, although milkweed was not specifically tested in this module of the experiment.
Boutin et al. (2010)	Two glyphosate formulations, Round-Up Original and Vision, were used at the label rate. A non-ionic surfactant, Agral 90, containing nonylphenoxy polyethoxyethanol was added to the formulation, as recommended on the label. Glyphosate was tested on 15 broad-leaf species, which included 3 crops and the rest were wild species. Milkweed was not included.
SERA (2010)	This study was conducted with a number of glyphosate formulations such as 80WDG, 75% a.i.; 80WDG, 48.3% a.i.; CP-70139, IPA, 50% a.i. Tests were conducted on crops. Milkweed was not included.

Boutin et al. (2012)	Crops and wild species were tested with formulated glyphosate products, including Round-Up Original. Milkweed was not included.
Allison et al. (2013)	This study tested the impact of the glyphosate formulation Vision, containing 356 g ae/L (acid equivalent per liter), on crop and non-crop species under high and low organic content soil. A non-ionic surfactant Agral 90 was used based on the label recommendation. Toxicity was tested with up to 73% of the maximum label rates. Milkweed was not included.
Boutin (2013)	List of endpoints (IC_{25}) for 70 plant species, mostly wild species. Plants were tested with Round-Up Original or Vision at 100% label rate. Milkweed was not included. The list is saved as PMRA # 2440641. Detail of the study protocol is available in PMRA # 2440646.
Boutin (2014)	List of all the plant species used for the PMRA SSD calculation, tabled and converted to IC_{50} by C. Boutin. This list is also reported in PRVD2015-01, Table X.14.
Unpublished studies	Chetram and Lucash (1994) (PMRA 1164982), Harnish (1994) (PMRA 1161847) and Everett et al. (1996) (PMRA 1213260), Bramby-Gunary (2012a) (PMRA 2211852); Bramby-Gunary (2012b) (PMRA 2211858)

4) USEPA (1993) suggests the need for labelling requirements for endangered species to mitigate risks, which the PMRA does (*sic*) not consider and furthermore, the efficacy of labelling to mitigate risk must be questioned.

The cited US EPA review indicates that endangered plant species may be at risk from the use of glyphosate. It also mentions that EPA provided guidance regarding endangered species precautionary labelling, but details of such labelling are, however, not reported in the document.

To further support their comment, the objectors also provided information on the status of monarchs in Canada reported by the Committee on the Status of Endangered Wildlife in Canada (COSEWIC). The monarch butterfly is designated as an endangered species in Canada. The monarch butterfly is also found in the United States and in Mexico given the migratory patterns of this species; however, the monarch is not considered endangered in these countries. Also, milkweed is not designated as endangered in North America even though it is considered a key food sources for monarch larvae.

While PMRA acknowledges that the monarch butterfly is currently listed as endangered in Canada by COSEWIC, the PMRA did not conduct a separate assessment for endangered species; the PMRA assessment protects all species, including species at risk. The protection of endangered species is managed in Canada through other initiatives, for example:

- The Canadian *Species at Risk Act* (SARA, 2003) establishes a legislated process for the assessment, listing and recovery of species at risk (Environment Canada 2007) and included general prohibitions and provisions for enforcement.
- The *Canada National Parks Act* protects the monarch at Point Pelee National Park in Ontario.

- *Fish and Wildlife Conservation Act* (1997, Province of Ontario) gives "special status" to a number of invertebrate species, including the monarch butterfly.
- Canada and Mexico signed declaration creates an International Network of Monarch Butterfly Reserves (1995). Three areas in Southern Ontario were designated as Monarch Butterfly Reserves under the declaration: Point Pelee National Park, Long Point National Wildlife Area and Prince Edward Point National Wildlife Area.
- The North American Monarch Conservation Plan (NAMCP) offers a list of key trinational collaborative conservation actions, priorities, and targets to be considered for adoption by the three countries. (Commission for Environmental Cooperation, 2008)

Comment 7: A comment was received that states that PMRA falsely claimed that six other studies considered in the assessment included information on glyphosate's impact on milkweed and monarch (PMRA# 1161847, 1161848, 1169475, 1164892, 1213259 and 1213260; all registrant submitted studies):

"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. [...] 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."

PMRA Response

As indicated earlier, and consistent with the glyphosate documentation published by PMRA, White and Boutin (2007) was the only study that provided a milkweed endpoint. The basis of this comment is thus not completely clear. It is possible that these studies were made available to the objectors for completeness, as these are all unpublished (registrant-provided) studies related to the toxicity testing of glyphosate on plants.

Even though milkweed was not specifically tested in the studies cited by the objector, they were used to calculate a plant toxicity endpoint that is protective of 95% of plant species. The calculated endpoint was found to be protective of milkweed as the endpoint was more sensitive than milkweed endpoint. As such, the buffer zones calculated for glyphosate on the basis of this toxicity endpoint are expected to adequately protect milkweed found on the perimeter of the treatment area.

Comment 8: In addition to the detailed comments outlined above, this objection also provided an overall summary of the data deficiencies they identified with respect to the impact of glyphosate on milkweed:

- **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 that use in these targeted areas does not negatively affect milkweed and monarchs in their preferred habitats.**

PMRA Response

Guidelines for the testing of pesticides are developed and approved internationally by experts from the scientific community, and are the basis of the risk assessment in regulatory agencies worldwide. Test guidelines for plants specify that trials are conducted with a variety of different crop species, and there is scientific evidence indicating that crop species can be more or equally sensitive compared to wild species. While milkweed is not part of the representative test species used for pesticide registration, it was recognized as an important species to consider for the glyphosate re-evaluation and therefore the available milkweed endpoint was included in the assessment. Furthermore, as discussed earlier an SSD approach was used for the glyphosate assessment so that risk calculations and mitigation measures would be protective of 95% of all plant species. The resulting HC_5, which was used in buffer zone calculations, was more protective than the toxicity endpoint available for milkweed.

It is noted that milkweed was in fact tested with a formulated glyphosate product, as were several other plant species both crop and non-crop, and that the risk assessment explicitly addressed the relative toxicity of formulations compared to the technical grade active ingredient. Most of the plant toxicity data used in the assessment was related to the effects of glyphosate and its formulations on vegetative vigour, as this was mainly where effects were observed. Seedling emergence studies conducted on a battery of species showed that neither the glyphosate technical active ingredient nor its formulations are toxic to this stage of plant development. Therefore, it is reasonable to anticipate that similar results on the seed germination would be observed in milkweed.

With regard to the last bullet, it is worth noting that toxicity endpoint is derived from a standard dose-response test and is standard in all risk assessments. The exposure from drift and runoff is however taken into consideration in the assessment. Drift is considered by adjusting the application rate with the predicted spray deposition off the treated area, which varies according to the type of product and the application equipment. Runoff is estimated using modelling.

Comment 9: Milkweed decline in agricultural regions affects 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." To support this, the objectors provided information relative to milkweed declines observed in certain agricultural regions of the United States and cited research that links this decline to glyphosate use. The objectors also argued that extensive use of glyphosate on herbicide-tolerant crops can further increase milkweed decline and reduce fecundity in monarch females. The objector concluded by stating that **"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 monarch habitats in its decision."**

PMRA Response

In Canada, milkweed within agricultural fields is generally considered to be a pest that can be treated with herbicides. PMRA develops buffer zones that are intended to protect non-target plants on field margins, including milkweed. A similar comment about the decline of milkweed in agricultural fields due to the use of glyphosate was received during the consultation period for the glyphosate re-evaluation. The response provided in RVD2017-01 is reiterated below in italics, as it is also relevant here.

> *"Monarch butterflies (Danaus plexippus) rely completely on plants in the milkweed family, especially the common milkweed (Asclepias syriaca) for both reproduction and larval food. Until recently, this plant was readily found in the Midwestern Corn Belt of the US and southern latitudes of Canada.*
>
> *Monarch habitat has been documented to be in decline for the last 20 years in North America (Pleasants and Oberhauser, 2012, Brower et al. 2012, Bhowmik, 1994). Before the introduction of GMO crops, glyphosate was applied in spring at the pre-emergence stage of crops and had limited impact on the survival of the common milkweed (Waldecker and Wyse, 1985, Doll 1998). But recent introduction of GMO crops resistant to glyphosate enables herbicide treatments to be done very late in the growing season (Carpenter and Gianessi, 1999 and Duke and Powles, 2008), impacting the last emerged shoots of the common milkweed, and thus, compromising its survival.*
>
> *For the monarch, the decline in milkweed represents a threat since the plant is now incapable of re-colonizing fields after GMO crop harvest, especially in the corn belt of*

the USA and now in the low latitude fields of Canada. The discussion is open as to what the grower should do regarding the competition of the milkweed and other weeds against his own crop within a specific field and/or the protection of the milkweed within the same field.

In fact, glyphosate is not meant to destroy monarch habitats outside of field limits. This is why buffer strips along agricultural fields close to hedgerows and other terrestrial and aquatic habitats exist, and why buffer zones are required to mitigate the impact of drift on non-target organisms located in aquatic and terrestrial habitats. In addition to agricultural pressures, Monarch habitat is also threatened by natural disasters (fire, drought, flood, etc.) and urbanization.

Canada is working with the US and Mexico to coordinate Monarch conservation efforts and is a member of the Trinational Monarch Science Partnership; the government of Canada's participation is led by Environment and Climate Change Canada. Domestically, the federal government has posted its proposed management plan for Monarch on the Species at Risk Public Registry, is funding research on Monarch habitat, and is using its Species at Risk funding programs to support Monarch and pollinator conservation."

Overall, the opposing body of evidence with respect to the state of monarch populations and the factors affecting it outside the agricultural fields highlights the complexity of this question. The PMRA is of the opinion that buffer zones are an appropriate mitigation strategy for the protection of milkweed outside of cropped areas, which falls within the PMRA's mandate. Other broader strategies for the conservation and management of monarch habitats in Canada are led by other governmental and non-governmental bodies, as per their respective legislation and mandates.

Comment 10: Reduced availability of nectar along roadsides affects fall migration

"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. [...] roadside maintenance in Canada involves herbicide spraying which limits nectar-producing flowering vegetation along crucial corridors. [...] The PMRA's Decision has failed to develop use limitation guidelines consistent with the monarch management plan published by Environment and Climate Change Canada (ECCC). At the very least, the PMRA must integrate the recommendations in the proposed management plan 2014-2019, and cannot defend continued inaction on risk mitigation strategies by calling for future research, especially when strategies have already been proposed by other federal Ministries in Canada."

PMRA Response

In support of this claim the objection cited Inamine et al. (2016) and Environment Canada, 2014 Management Plan for the Monarch in Canada. Both were reviewed.

PMRA acknowledges that nectar sources are vital to monarchs during their fall migration and that flowers found along roadsides can be an important source of nectar. Monarchs are not dependent on milkweed during fall migration (milkweed is not flowering in the fall), but rather rely on a variety of nectar producing plants to support their energy requirements during this period. For example, monarchs are known to forage on plants from the Asteraceae and Fabaceae families (e.g., goldenrods, gayfeathers, frostweed, sunflower and alfalfa).

Inamine et al. (2016) report a monarch population decline in Mexico and conclude that this decline is most strongly driven by events occurring after the period where monarchs rely on milkweed. The authors do not specifically identify the cause of this decline, but indicate that the negative impact on populations has been increasing annually and is impacting the monarch population prior to the time they reach Mexico. Some of the factors that could be responsible for the migratory decline include a severe 100-year drought in Texas (2010–2015), predator, parasitoid and disease impacts, sub-lethal insecticide effects in the breeding grounds or lack of nectar sources during the fall (Brower et al, 2006; reference therein Inamine et al., 2016). Inamine et al. indicate that uncovering the cause of the trends at the migratory stages may be critical to understanding the decline in Mexico.

The research submitted by the objectors however does not show a clear correlation between glyphosate use, nectar-producing flowering vegetation and monarch decline. And while there are several hypotheses to explain the decline, none have been proven or investigated further.

The monarch management plan cited by the objector discusses threats to the monarch and identifies broad strategies and conservation measures for the monarch. While the use of herbicides is identified as a threat to breeding and nectaring habitats, there are no conservation measures associated directly with herbicide use.

Glyphosate product labels require the use of buffer zones to protect habitats adjacent to the treated sites. Further restriction may be imposed by other Acts or jurisdictions. For example, the *Species at Risk Act* (SARA) provides protection for all species listed as endangered, threatened or extirpated, and protects the critical habitat of these species when they occur on federal lands. Under SARA, the Canadian government develops management plans that set conservation goals and objectives, identify threats to species, and indicate the main areas of activities to be undertaken to address those threats. Other conservation efforts are also ongoing, as cited in the previous PMRA response related to the monarch, which is cited further above.

Comment 11: Failure to consider critical evidence associated with glyphosate's impact on soil microbiome

"Adverse effects of glyphosate on soil microbiome were not addressed. PMRA indicated that this was beyond the scope of pesticide assessment, but this is contrary to the most recent understanding of the importance of soil microbiome on plant and soil health. Neglecting such aspect may lead to eventual yield reductions as there may be alterations in diseases and nutrients available in the fields."

PMRA Response

PMRA is aware of interactions between soil microorganisms, plant nutrition and plant health. A similar comment was received during the consultation period for the glyphosate re-evaluation. The response provided in RVD2017-01 (Appendix I, p. 48) is reiterated below, as it is also relevant here.

> *"Although the PMRA is aware that interactions between soil bacteria, fungi and plant root systems can improve plant health, the PMRA does not assess risks to soil microorganisms. Negative impacts have been observed on specific soil microbe strains, but overall, evidence suggests glyphosate end-use products have a low impact on deleterious and beneficial soil microbes following application. Glyphosate contributes to sustainable agricultural systems by reducing the need for cultivation (for example, no-till technique), increasing plant biomass on the ground, increasing the soil organic matter content, improving soil structure and reducing soil erosion and run-off. The fact that glyphosate use has been increasing since its first registration in Canada in 1976 demonstrates that growers have adopted the use of glyphosate and in turn the use of glyphosate-resistant crops very rapidly. If glyphosate had a meaningful negative impact on soil microbial activity over this 40 year use history, growers would not have been so quick to adopt and continue to use the product. The effects on soil microflora would have the strongest impact on crops grown on the fields. Areas away from the site of application are not likely to be negatively impacted."*

Even though this question was previously addressed by PMRA, the information provided in the notice of objection (NoO) was examined to determine whether the current information provide compelling evidence that impact the validity of the glyphosate risk assessment document or previous PMRA response. Other sources of information were also consulted, for completeness.

As is the case in susceptible plants, glyphosate can also be toxic to sensitive bacteria and fungi through the inhibition of the enzyme enolpyruvylshikimate-3-phosphate synthase (EPSPS) in the shikimate pathway. Only some fungi and a limited number of microorganisms have the EPSPS target site that could be affected by glyphosate (Duke and Lydon et al., 2012). Examples of species affected by glyphosate are provided in the NoO report. It is therefore recognized that the use of glyphosate could cause a shift in the assemblage of the soil microbiome given this selective sensitivity. Of course, such a shift can occur with other herbicides as well.

Evidence suggests that some soil functions remain unaffected even though the use of glyphosate may change the assemblage of the microbiome. For example, several sources indicated that repeated glyphosate applications are unlikely to severely reduce the ability of soil microbial communities to metabolize glyphosate (Arregui et al., 2003 and Doublet et al., 2009, referenced in Duck and Lydon et al., 2012). Studies using ^{14}C-labeled glyphosate showed that the production of $^{14}CO_2$ (mineralization formed as a result of biotransformation) begins after addition of glyphosate to soil without a lag period, suggesting that microorganisms that can degrade glyphosate remain available in soil despite the use of this herbicide (Duke and Lydon et al, 2012). Also, effects of glyphosate could be temporary (Nye et al., 2014). This may be due to the low persistence of glyphosate in soil (glyphosate transforms both with and without the presence of soil microbes), combined with its strong adsorption behaviour; this would cause concentrations of glyphosate in soil solution to rapidly decrease, and thus negative effects on the microbiome to be short-lived.

In addition, Duke and Lydon et al. (2012) concluded that broad spectrum measures of microbial activity (respiration and enzyme activities) and community structure show inconsistent or no response to glyphosate use, and no significant adverse secondary effects of glyphosate have been established during its several decades of use of glyphosate over vast areas. Santos and Flores (1995) showed that glyphosate use at field recommended rates (0.2 - 4 kg/ha) has no negative effects on the soil microbiome, including members of the genus *Azotobacter* (important nitrogen fixing bacteria found in a variety of soils worldwide). Also, while Newman and Hoilett et al. (2016) observed effects of glyphosate on the specific bacterial taxonomic groups, there were no changes in the overall bacterial community diversity. Newman and Lorenz et al. (2016) concluded that glyphosate could change gene expression in soil bacteria, but provided no information on whether the shift on bacterial taxa or activities affects the functional capability of the soil.

Some of the reviewed information was specifically related to the effects of glyphosate on the soil microbiome of glyphosate resistant (GR) crops. While the available information indicates that the use of glyphosate can cause complex and varied responses in soil microbes, none of the sources reviewed show a clear correlation between glyphosate use and plant or soil health. Some studies (Kremer and Means, 2009; Zobiole and Kremer et al., 2011; Newman and Hoilett et al., 2016; Newman and Lorenz et al., 2016) indicated that glyphosate caused adverse effects on mineral nutrition, microbial species/community and microbial activities in the soil of GR crops. However, a literature review of more than 8000 relevant peer-reviewed papers (Duck and Lydon et al., 2012) did not support the view that glyphosate use in GR crops negatively impacts the soil microbiome or increases crop disease or crop productivity. These conflicting results on the effects of glyphosate exposure on the soil microbiome could be entirely or partly due to differences in the soils, climatic conditions, and/or GR cultivars used in the studies. As well, the wide range of species sensitivities in microbial communities and many other spatial and temporal factors can affect the soil ecology (Santos and Flores, 1995), which makes it difficult to generalize results obtained in any given study.

One study cited by the objector speculated that glyphosate exuded from roots of GR soybeans may serve as a nutrient source for fungi, such as *Fusarium spp*, and this can in turn stimulate propagule germination, which may have pathogenic impact on plants (Kremer and Means, 2009). However, the mechanisms of these glyphosate-mediated increases in root infection in GR soybeans remain unknown and the study did not establish that these root exudates specifically stimulated the growth of *Fusarium spp.* The latter fungi are known to exist in soil saprophytically and are widespread in rhizospheres of many plants. Most species are harmless and are relatively abundant members of the microbial communities. Some species, however, produce mycotoxins and could become pathogenic to plants.

Other cited research suggests that glyphosate-induced effects on the soil microbiome can affect plant nutrition. For example, Zobiole and Kremer et al. (2011) conducted research related to the effects of glyphosate on the availability of manganese for plant uptake. Manganese is important for plant photosynthesis and amino acid synthesis. The authors reported that glyphosate negatively impacts the rhizosphere complex interactions of microbial groups, biochemical activity and root growth of GR crops, and that this can have subsequent detrimental effects on plant growth and productivity. They claimed that glyphosate increases the ratio of manganese oxidizer bacteria relative to manganese reducer bacteria in rhizosphere soil. Because the manganese oxidation lowers the solubility of manganese, the authors concluded that glyphosate decreased the availability of manganese for plant uptake. It is noted, however, that this study was conducted in a greenhouse during a relatively short period and therefore does not reflect actual field conditions where GR cropping has now been extensively used in the major agricultural regions for over 15 years. Yield data for crops that are now predominantly GR cultivars do not support the view that there are significant mineral nutrition or disease problems with GR crops (Duke and Lydon et al., 2012).

Overall, the cited data does not provide any information or indication that the shift in bacterial taxa affects the functional capability of the soil under glyphosate-tolerant cropping. Globally, the use of glyphosate and adoption of the GR crops has been rapid. Thus, if there were any significant mineral nutrition and/or disease problems with these crops, it is expected that the problems would be manifested in yield reductions and farmer dissatisfaction. Yield data from before and after the introduction of GR crops are reported to show similar trends. While there could be isolated pockets of adverse effects due to the use of glyphosate on GR crops that would be masked by their general success, such cases have not been conclusively documented. Overall, it appears that in GR crops, the baseline disease resistance or susceptibility of the host plant, not the presence of the glyphosate resistance gene or treatment with glyphosate, is the major contributor to susceptibility (Duke and Lydon et al., 2012).

Comment 12: Failure to consider critical evidence associated with glyphosate's chelation effects on nutrient and toxicant levels in soils.

"Glyphosate binds (chelates) with vital minerals in soils and plants. Crops treated with glyphosate may therefore contain higher levels of metals, including cadmium. Although this is still an active scientific debate, PMRA should consider the growing body of literature related to chelation."

PMRA Response

PMRA does not currently assess the risk of the chelating potential of pesticides; however, the information provided in the NoO relevant to this comment was examined to determine whether it provides compelling evidence impacting the validity of the glyphosate risk assessment document.

Barański et al. (2014) was the only study cited by the objectors to support the point that crops treated with glyphosate may contain higher levels of cadmium. This study however contains no information specifically related to the use of glyphosate. The authors instead compared organic farming with conventional farming. A lower concentration of cadmium was observed in organic crops, which was linked to specific agronomic practices in organic farming (abstract, p. 794). The difference between the two systems with respect to higher levels of cadmium was mainly linked to the use of fertilizers.

The objectors themselves acknowledged that there is a scientific debate as to whether glyphosate could chelate with vital minerals in soils or induce the mobilization of heavy metals, and by extension, affect their uptake in plants. Given that the NoO cited reference was irrelevant to the subject matter, several other references were reviewed by the reviewer to illustrate this issue and are discussed here.

Glyphosate is known to be a relatively weak metal cation chelator (Madsen et al., 1978; Wang and Stone, 2008). Because of the chelation ability of glyphosate, it has been assumed to affect the uptake of trace nutrients in plants, such as metals. However, while this may be true for a strong chelator, none of the available research indicates that a weak chelator such as glyphosate would mobilize metals and as a result increase the plant uptake of micronutrient cations from the soil (Duke and Lydon et al., 2012). In addition, glyphosate degrades quickly and is adsorbed to soil rather than remaining in solution where it can complex with metal ions. Even during the short period after application where glyphosate is present in the soil solution, the metal cations are not necessarily free ions to bind with glyphosate, as they can form complexes with dissolved soil organic matter and other ligands (Weng et al., 2001; referenced in Duke and Lydon, et al. 2012).

Given the fact that glyphosate is only a weak chelator, and also taking into consideration the fate and behaviour of glyphosate in soil, it is not expected that glyphosate will significantly affect the uptake of metals by plants in most situations.

Comment 13: Inefficiency of risk mitigation measures for runoff and leaching

"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."

PMRA Response

The expressions vegetative buffer strips (VBS) and buffer zones were used interchangeably in the NoO report, likely as a result of the different nomenclature used in the scientific literature or between regulatory agencies. Similarly, the terms runoff and leaching were also used as synonyms in some cases. In order to ensure that there is no confusion when addressing the concerns raised by the objectors, definitions are provided below for clarity. It is also noted that PMRA employs the expression of vegetative filter strips (VFS) rather than vegetative buffer strips (VBS).

During and after application, a pesticide can move through the environment by several routes, such as spray drift, runoff and leaching. Spray drift is defined as the wind-induced movement of spray particles (droplets) away from the spray swath during application. Runoff is the movement of soil particles or water containing the pesticide into surface water systems. Leaching is the vertical movement of the pesticide through the soil profile which can lead to the pesticide entering groundwater. If a risk is identified during the assessment, then various mitigation strategies are implemented to reduce it.

A buffer zone is defined as a no-spray area required between the point of direct application and the closest downwind edge of sensitive habitats (which contain non-target species), and are calculated using recognized drift models. Buffer zones reduce the amount of pesticide reaching non-target habitats via spray drift, and risk is reduced to an acceptable level as a result of the decreased exposure.

Vegetative Filter Strips (VFS) are areas of permanent vegetation intended to intercept and slow runoff, thereby reducing the amount of pesticide reaching surface water systems. VFS are suggested by the PMRA as a non-mandatory best practice on all agricultural product labels.

When leaching is identified as a potential route of dissipation, the product label will include information that can help the user identify and avoid circumstances where leaching can occur.

Spray drift and buffer zones:

The first concern raised by the objectors with respect to the glyphosate mitigation measures is related to buffer zones. According to the objectors, PMRA is claiming that buffer zones will reduce runoff or leaching, and different excerpts from the PRVD and RVD are cited to support this understanding. They state: **"PMRA fails to provide scientific evidence supporting the efficiency of buffer zones in mitigating glyphosate leaching to aquatic ecosystems. [...] PMRA's 2005 agricultural buffer zone document explicitly states that it only considers spray drift and not post application runoff and leaching."**

This concern appears to be due to a misinterpretation of the information provided in the public documentation on glyphosate. It is correct that the only purpose of buffer zones is to reduce the amount of spray drift entering a sensitive habitat. The citations provided by the objectors do not contradict this interpretation. This comment pertaining to the efficiency of buffer zones as a mitigating measure for runoff and leaching is therefore not considered further.

Runoff and vegetative filter strips:

The objectors state that the efficacy of vegetative filter strips is not well supported for glyphosate and cited several studies to support their claim. It is important to understand that risks to aquatic systems from runoff are considered to be acceptable by the PMRA without considering the use of VFS. For glyphosate, the risks from runoff were first assessed using modelled estimates of concentrations entering water systems via runoff and were further characterized, using water monitoring data. The monitoring data show glyphosate concentrations are relatively low in surface water despite more than two decades of glyphosate use. The recommendation of VFS is a non-mandatory best practice on all agricultural product labels.

In general, all the cited studies demonstrate that relatively narrow filter strips can be an effective mitigation tool to reduce the concentration of glyphosate in surface runoff. However, when studies conclude that VFS reduce the amount of glyphosate entering aquatic ecosystems, the objectors argue that results are not representative of real life conditions (Lin et al, 2011; Syversen and Bechmann, 2004; Syversen 2005). The other cited study was conducted in more realistic conditions (Hénault-Ethier et al., 2017) and the objectors claim that this study supports limited efficiency of VFS to minimize the runoff of glyphosate. However, this study reported that 28 - 56% of the glyphosate was actually trapped in soil; this is interpreted by the reviewer as demonstrating the efficiency of the VFS. The low concentrations of glyphosate in the runoff water compared to soil was attributed by the authors to limited statistical power and challenges experienced in collecting runoff samples under the heterogeneous distribution system. The objectors failed to take into account other statements from the study authors indicating that despite the limitations associated with the water sampling, they were confident that results were comparable to other studies conducted by Lin et al. (2011) and Syversen and Bechmann (2004), based on the amounts trapped in soil.

Lin et al. (2011) suggested that a VFS of four metres significantly reduced the transport of dissolved and sediment-bound glyphosate in the surface water by 60 to 71%. A fine-textured soil was used in the study and the authors concluded that wider strips may be required to trap the finer particles more effectively. It is noted, however, that larger strips may not be needed in other types of soils since glyphosate is known to have a strong tendency to adsorb to soil.

The study by Syversen and Bechmann (2004) supported that VFS composed of various grasses are effective for glyphosate retention. However, the average total removal efficiency for glyphosate was less than that of other pesticides used in the experiment. The authors associated the low efficiency of VFS for glyphosate to the type of the soil used in the study (silty clay loam soil), suggesting that fine particles such as silt have lower efficiency comparing to the coarser particles in trapping glyphosate.

The study by Syverson (2005) demonstrated that a VFS of five metres reduced the runoff by 61% and 78% for glyphosate and AMPA (aminomethylphosphonic acid), respectively. AMPA is the glyphosate major transformation product, which is also known to bind to soil.

One of the criticisms expressed by the objectors with respect to the above studies was related to the use of a homogeneous runoff distribution system, which is unlikely to reflect the more heterogeneous natural conditions. A homogenous distribution system however facilitates experimental manipulations and replication. Using a homogeneous runoff distribution system, Lin et al. were able to obtain similar results over two different years (2004 and 2006). With a relatively large sample size (48 aqueous and 48 sediment samples during each year), results indicated that VFS treatments significantly reduced the load of glyphosate in surface runoff. A more homogenous system also allows a comparison of results from different studies, as was done in by Syversen and Bechmann (2004) and Syversen (2005). Conversely, the field study of Hénault-Ethier et al. (2017), conducted under heterogeneous field conditions, showed significant variations in the results. While more realistic, this can also complicate the interpretation of results. This study investigated the efficiency of a three metre VFS which is recommended by the Quebec provincial government. According to the objectors, this study indicated that VFS have a very low or weak potential of effectively minimizing glyphosate and AMPA in runoff water; while 28 - 56% of the glyphosate was reported trapped in soil. The authors recommended that the soil samples, instead of runoff water be used as an indicator of efficiency when studying VFS. The reviewer noticed that there were challenges with the sampling due to the site conditions. In some occasions the number of collected samples was limited to only one, samples were lost, and samples from one of the two test sites were completely excluded from the analysis.

The objectors argue that wide VFS are not often accepted by farmers and are a cause of frustration given their negative economic impacts. In general, all the above studies demonstrate that relatively narrow filter strips can be an effective mitigation tool to reduce the concentration of glyphosate in surface runoff. Hénault-Ethier et al. (2017) specifically indicate that the width is not necessarily the determining factor when assessing the efficiency of VFS for glyphosate which has a high adsorption tendency.

Overall results of the cited references show that VFS, regardless of its size, will in fact contribute to the reduction of glyphosate entering surface water systems by reducing the speed of runoff and allowing it to bind to soil and settle. Runoff statements, including information regarding VFS, appear on glyphosate product labels to inform users of best management practices to reduce pesticide exposure. In conclusion, although the risks of glyphosate were determined to be acceptable without VFS, the cited references support that the voluntary adoption of VFS further reduces the potential of glyphosate entering surface water systems through runoff.

Comment 14: Leaching assessment:

The objectors claim the PMRA also failed to consider scientific evidence concerning glyphosate's potential to leach into groundwater. 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. 2017). […] The rare detections of glyphosate in Canadian groundwater may be due to low sampling size; glyphosate is known to be present in groundwater 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, 2017)

A leaching assessment was conducted during the glyphosate re-evaluation to support the human health assessment, which takes into account the contribution of drinking water to overall dietary risks. Given its strong adsorption to soil particles and its short half-life in the environment, glyphosate is not expected to move downward through the soil to enter groundwater. This is confirmed by drinking water modelling results which indicates negligible concentrations of glyphosate in ground water. The human health assessment identified no risks of concern from a drinking water perspective.

The study of Hénault-Ethier et al. (2017) was examined and is discussed above. The hypothesis that the use of VFS may increase glyphosate infiltration in groundwater was not tested in this study. Furthermore, the experimental design and statistical analysis of the study have several limitations which make it difficult to make a meaningful and reliable conclusion from the results.

The objectors stated that rare detections of glyphosate in Canadian groundwater reported in PMRA public documents is due to low sampling size, and cited Horth and Blackmore (2009) to support their claim. This study relies on more than 36,000 groundwater samples from 9,000 sites from 1993-2009. Upon examination of this study, the reviewer found that the authors of this study concluded that there is no evidence of any persistent and confirmed groundwater contamination with glyphosate or AMPA. Furthermore, the authors stated that detections that meet the European threshold of >0.1 $\mu g \cdot L^{-1}$ seem to occur in shallow water or spring water, which is often included in groundwater surveys but not representative of actual groundwater systems.

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Comment 15: A comment was received that made the assertion that the US EPA ongoing review of glyphosate is compromised due to alleged interactions between Monsanto and EPA. Subsequently, that Health Canada's review of glyphosate is also compromised due to collaboration between Health Canada and EPA in the review of glyphosate.

PMRA Response:

The Glyphosate Re-evaluation Decision Document (RVD2017-01) published by Health Canada on April 28, 2017, is unrelated to alleged interactions between Monsanto and EPA. Although PMRA and EPA scientists did collaborate on the assessment of publically available literature for glyphosate, PMRA conducted its own independent assessment of any registrant-submitted information without EPA involvement, and overall assessments were conducted separately. PMRA also conducted its own independent risk assessment for glyphosate and determined the appropriate risk management options based on the outcome of its scientific review. Regulatory decisions were also taken separately in each country.

Comment 16: A comment was received that made the assertion that studies cited in Health Canada's published reference list for the final re-evaluation of glyphosate, are implicated in alleged misconduct, or have authors implicated in other alleged misconduct. The assertion questions the independence of some of the scientific review articles for glyphosate.

PMRA Response:

Health Canada's evidence-based re-evaluation decision considered relevant data and information from multiple registrants, published scientific reports, federal and provincial governments, and other regulatory agencies. In excess of 1,300 relevant scientific studies were considered for the glyphosate re-evaluation and were detailed in the Reference List section of both the proposed and final re-evaluation decision documents issued by Health Canada.

Most of the review articles, which are referenced as problematic in the letter from Ecojustice dated October 29, 2018, were published **after** Health Canada published the Proposed Re-evaluation Decision (PRVD2015-01) in 2015. In addition, the review articles themselves, are not actual studies, but a summary of several individual studies.

Of main importance is that Health Canada scientists had access to the individual studies, including the raw data underpinning those studies, during the re-evaluation of glyphosate. Within each individual study, Health Canada scientists were able to review and conduct their own analyses of the raw data. The actual review of the individual studies was completed by Health Canada scientists prior to the release of most review articles noted in the letter.

With regard to the endpoints of concern highlighted within the NoO, it is important to note that there were many additional studies examined by Health Canada scientists that were relevant to the subject areas of interest, but were not considered in the review articles cited. For example, the review article on cancer studies included 14 studies, while Health Canada had access to approximately 20 studies, including the 14 cited in the review article. The review article on genotoxicity was based on approximately 25 studies for glyphosate (technical) while Health Canada had access to over 100 studies on glyphosate (technical), including the 25 cited in the review article. (Additional examples are shown in the attached table)

During the consultation period following publication of the PRVD for glyphosate, extensive comments and information were received from various stakeholders including registrants, growers, non-governmental organizations and the public. The review articles cited within the Ecojustice letter were considered during the response to comment period, however, these review articles in no way affected the final outcome of the re-evaluation published in RVD2017-01 or PMRA's risk conclusions regarding the continued registration of glyphosate. When summary review documents are provided, as a matter of practice, Health Canada ensures that underlying studies upon which these reviews are based, along with the raw data, have also been examined. The references in the final Re-evaluation Decision document subsequently list all additional information that were assessed.

Although the assertion with regard to improper or misleading citations is disconcerting, and is being examined by Health Canada officials, the review articles themselves did not alter the final decision.

While considered during the response to comment period, these review articles did not impact the final decision regarding continued registration of glyphosate.

Aspect of Review	**Data - Review papers relied on**	**Data - PMRA relied on**
Animal Carcinogenicity	Greim et al. (2015) examined 14 studies	Approximately 20 carcinogenicity study – including the ones examined by Greim et al. (2015)
Genotoxicity	Brusick et al (2016) examined about 25 studies for the glyphosate technical	Over 100 studies for the glyphosate technical – including the ones examined by Brusick et al. (2016)
Epidemiology studies examining cancer outcomes	Acquavella et al. (2016) conducted systematic review of the epidemiology data related to NHL and multiple myeloma	Over 50 cancer epidemiology data – including those reviewed by Acquavella et al. (2016)
Systematic toxicology and epidemiology review	Williams Kroes and Munor, (2000) examined over 50 studies of toxicology and epidemiology conducted up to the year 2000	Over 200 toxicology and epidemiology studies up to the year 2017 – including those reviewed by Williams Kroes and Munor (2000)
Developmental and Reproductive studies in animals Epidemiology studies examining reproductive and developmental outcomes	Williams et al. (2012) examined about 40 studies	Over 200 developmental, and reproductive toxicity studies in animals as well as all epidemiology data – including those examined by Williams et al. (2012)
Epidemiology studies on applicators	Solomon et al. (2016) about 10 studies in applicators	Over 50 epidemiology studies including those examined by Solomon et al. (2016)