VANCOUVER CALGARY TORONTO OTTAWA HALIFAX

ecojustice

Laura Bowman
1910-777 Bay Street, PO Box 106
Toronto, Ontario M5G 2C8
Tel: 416-368-7533 ext. 522
Fax: 416-363-2746
Email: lbowman@ecojustice.ca
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October 27, 2022

Frédéric Bissonnette
Director General - Chief Registrar
Pest Management Regulatory Agency
Health Canada

sent by email to: frederic.bissonnette@hc-sc.gc.ca

Dear Mr. Bissonnette:

Re: Calling for suspension of all renewals of glyphosate products until PMRA review of new science and evaluation of risks

This request is sent on behalf of Ecojustice, Canadian Association of Physicians for the Environment, Environmental Defence, the David Suzuki Foundation, Friends of the Earth, Prevent Cancer Now, and Safe Food Matters Inc. These organizations have a significant history of engagement with the PMRA on glyphosate regulation.

The PMRA's most recent assessment of the human health and environmental risks of glyphosate took place prior to 2015 and was finalized in 2017. As noted in previous correspondence with the PMRA, the 2015 proposed re-evaluation and the 2017 final re-evaluation contained major gaps. Since that time, there have been significant developments in the science around glyphosate risks.

We note that a large number of glyphosate technical active and end-use products are up for renewal at the end of 2022. The PMRA has indicated that it intends to take a "continuous oversight approach" to take action to identify and address health and environmental risk "sooner".[1] The PMRA has proposed a "continuous oversight lifecycle approach" which includes expanding and formalizing the use of data throughout the pesticide's regulatory life cycle to make better informed regulatory decisions and engage in "timely assessment and management of risks".[2]

[1] PMRA program renewal. https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/pest-management-regulatory-agency/program-renewal.html
[2] How we are transforming the Pest Management Regulatory Agency https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/pest-management-regulatory-agency/transforming/how-we-are-transforming.html

In this spirit, we are writing to request that the PMRA consider up-to-date science in evaluating glyphosate registration renewals and to ask that no renewals be granted until up-to-date science has been reviewed. Renewals are an amendment to the term of registration and as such trigger the PMRA's obligations to conduct a scientifically based assessment of acceptable risk under section 7 of the *Pest Control Products Act*. It is the registrant's onus to establish that glyphosate poses acceptable risks in light of the newly published science on the potential risks of glyphosate under the *Act* as well as any incidents that have been reported since the most recent evaluations in their renewal requests. Under subsection 16(2) of the *Pest Control Products Regulations*, the registrant must provide information on the risks posed by the product in a renewal application. The registrant is required to include a statement that the information provided is accurate and complete. The PMRA must evaluate this information and determine whether it has reasonable certainty that no harm will occur to the environment or human health from the renewals of glyphosate registrations. The environment encompasses more than just direct toxicological effects and includes the potential for increased emissions of pollution such as greenhouse gases and phosphorus, as well as impacts on endangered species such as monarch butterflies.

A review of the PMRA's 2017 glyphosate re-evaluation decision revealed that, despite there being no shortage of recent studies, the agency had assessed glyphosate's toxicological dangers on the basis of 118 industry documents that had not been peer-reviewed or published in academic journals, 80.5% of which pre-dated 1996.[3] A range of new research which the PMRA did not consider in the 2015-2017 decisions on glyphosate was raised by Ecojustice, Friends of the Earth, David Suzuki Foundation and Environmental Defence in a letter to the Minister of Health dated February 17, 2022. To our knowledge the PMRA has not updated the risk assessment of glyphosate to reflect this research, and, (with the exception of the Safe Food Matters notice of objection which was remitted back to the PMRA by the Federal Court of Appeal) the PMRA has declined to revisit all prior notices of objection to the 2017 re-evaluation decision of glyphosate or to consider new information post dating the 2017 re-evaluation decision.

As the PMRA lacks reasonable certainty that no harm will occur in light of recent published research:

- The PMRA should not renew glyphosate registrations that expire at the end of 2022.
- Any glyphosate registrations that have already expired must be the subject of a new application to register.

This letter should be considered an initial submission on this issue that is prepared in relation to the upcoming renewals of glyphosate products.

[3] Vandelac, L. and Bacon, M.-H. "Avis d'objection à la décision de réévaluation RVD2017-01 sur le glyphosate." Montréal: Université du Québec à Montréal (2017). Retrieved from cape.ca/wp-content/uploads/2017/08/Avis-d27opposition-ARLA-glyphosate-Vandelac-Bacon-juin-2017.-copie-C-1-1.pdf

Effects on the microbiome need to be better understood before glyphosate registrations are renewed

The PMRA needs to revisit the conclusion in the 2017 re-evaluation of glyphosate that "there is very little evidence" supporting potential impacts on gut microflora. Recent research on the potential adverse impacts of glyphosate-based herbicides on the microbiome needs to be evaluated by the PMRA prior to renewing glyphosate registrations. This research changes the weight of evidence concerning glyphosate's impacts on the microbiome. A recent study provides evidence that exposures to commonly used glyphosate-based herbicides at maternal doses of 1.75 mg/kg bw/day can modify the gut microbiota in early development, particularly before the onset of puberty. Several human and animal studies associate several diseases with early-life imbalances of gut microbiota. One line of evidence shows that traces of glyphosate in food may lead to alterations of gut microbiota, changes in the urine metabolome, and skin microbiota.[4] Studies forming part of this line of evidence include one that estimates that ~54% of human microbiome is sensitive to glyphosate based on analysis of the ESPS pathway, identifying a mechanism of microbiome disruption from glyphosate exposure.[5] Another concludes that there is "initial evidence that exposures to commonly used GBHs, at doses considered safe, are capable of modifying the gut microbiota in early development, particularly before the onset of puberty."[6] The microbiome is central in inflammatory bowel disease (IBD) and unfortunately Canada is a world leader for IBD in children 0-5 years old, with incidence increasing at 7% annually.[7] IBD

[4] Mao Q, et al. "The Ramazzini Institute 13-week pilot study on glyphosate and Roundup administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome" Environ Health. 2018 May 29;17(1):50. doi: 10.1186/s12940-018-0394-x; Leino L. et al. "Classification of the glyphosate target enzyme (5-enolpyruvylshikimate-3-phosphate synthase) for assessing sensitivity of organisms to the herbicide" J. Hazard. Mater. 2020;408:124556. doi: 10.1016/j.jhazmat.2020.124556; Motta E.V. et al. "Glyphosate perturbs the gut microbiota of honey bees". Proc. Natl. Acad. Sci. USA. 2018;115:10305–10310. doi: 10.1073/pnas.1803880115; Ruuskanen S. et al.. "Glyphosate-Based herbicides influence antioxidants, reproductive hormones and gut microbiome but not reproduction: A long-term experiment in an avian model" Environ. Pollut. 2020;266:115108; Bali Y.A., et. al. "Glyphosate based- herbicide exposure affects gut microbiota, anxiety and depression-like behaviors in mice" Neurotoxicol. Teratol. 2018;67:44–49. doi: 10.1016/j.ntt.2018.04.002; Mesnage R., et al. "Use of Shotgun Metagenomics and Metabolomics to Evaluate the Impact of Glyphosate or Roundup MON 52276 on the Gut Microbiota and Serum Metabolome of Sprague-Dawley Rats" Environ. Health Perspect. 2021;129:17005. doi: 10.1289/EHP6990; Blot N., et. al. "Glyphosate, but not its metabolite AMPA, alters the honeybee gut microbiota" PLoS ONE. 2019;14:e0215466; Mesnage R., Antoniou M.N. "Computational modelling provides insight into the effects of glyphosate on the shikimate pathway in the human gut microbiome" Curr. Res. Toxicol. 2020;1:25–33; Puigbò P, et. al. "Does Glyphosate Affect the Human Microbiota? Life" (Basel). 2022 May 9;12(5):707. doi: 10.3390/life12050707; Hu J., et. al. "Low-Dose exposure of glyphosate-based herbicides disrupt the urine metabolome and its interaction with gut microbiota" Sci. Rep. 2021;11:3265. doi: 10.1038/s41598-021-82552-2; Suppa, A., et al. "Roundup causes embryonic development failure and alters metabolic pathways and gut microbiota functionality in non-target species" Microbiome 8, 170 (2020). https://doi.org/10.1186/s40168-020-00943-5.

[5] Leino L, et. al. "Classification of the glyphosate target enzyme (5-enolpyruvylshikimate-3-phosphate synthase) for assessing sensitivity of organisms to the herbicide" J Hazard Mater. 2021 Apr 15.

[6] Mao Q, et. al. "The Ramazzini Institute 13-week pilot study on glyphosate and Roundup administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome" Environ Health. 2018 May 29.

[7] Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR, Vutcovici M, El-Matary W, Nguyen GC, Griffiths AM, Mack DR, Jacobson K, Mojaverian N, Tanyingoh D, Cui Y, Nugent ZJ, Coulombe J, Targownik LE, Jones JL, Leddin D, Murthy SK, Kaplan GG. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in

predisposes individuals to colorectal cancer, which is increasing by 7% annually in young adults.[8]

The PMRA's approach to carcinogenicity is out of date and has been found to be arbitrary and capricious by US courts

New lines of evidence have emerged providing additional links between glyphosate and cancers. A 2020 review by the highly experienced expert Professor Chris Portier included all of the animal carcinogenicity studies submitted to EFSA and to the EPA – evidence that the PMRA should evaluate, but to date apparently has not. The study concluded that there was clear evidence that glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas and malignant lymphomas in female CD-1 mice. There is clear evidence that glyphosate causes hemangiomas in female Swiss albino mice. There is clear evidence that glyphosate causes kidney adenomas, liver adenomas, skin keratoacanthomas and skin basal cell tumors in male Sprague-Dawley rats and adrenal cortical carcinomas in female Sprague-Dawley rats. There is clear evidence that glyphosate causes hepatocellular adenomas and skin keratocanthomas in male Wistar rats. There is some evidence that glyphosate causes malignant lymphomas in male and female and kidney tumors in male Swiss albino mice. There is some evidence that glyphosate causes testicular interstitial cell tumors in male Sprague-Dawley rats. There is some evidence that glyphosate causes pituitary adenomas in male and female Wistar rats and mammary gland adenomas and carcinomas in female Wistar rats.[9] In 2019 a meta-analysis concluded that evidence from experimental animals and mechanistic studies showed a compelling link between exposures to glyphosate-based herbicides and increased risk of non-Hodgkin's lymphoma (NHL).[10] A 2021 review provided coherent and compelling evidence that glyphosate and GBFs are a cause of NHL in humans exposed to these agents.[11] The PMRA has also not yet incorporated new information on genotoxicity.[12]

Moreover, results of a 2019 study suggest that glyphosate exposure promotes TET3-mediated global DNA hypomethylation in MCF10A cells. DNA hypomethylation is known to play a determining role in cancer development. The findings of this study revealed that low pressure but sustained DNA hypomethylation by way of TET pathway primes cells for oncogenic response in the presence of another potential risk factor such as diet, tobacco use,

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Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol. 2017.

[8] Dylan E. O'Sullivan, Robert J. Hilsden, Yibing Ruan, Nauzer Forbes, Steven J. Heitman, Darren R. Brenner, The incidence of young-onset colorectal cancer in Canada continues to increase,Cancer Epidemiology,Volume 69,2020.

[9] Portier, C.J. A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Environ Health 19, 18 (2020).

[10] Zhang, L., et. al. Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence. Mutation Research, (2019) 781, 181–206.

[11] Dennis D. Weisenburger, "A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of Non-Hodgkin Lymphoma," Clinical Lymphoma Myeloma and Leukemia, 21(9) (2021) https://doi.org/10.1016/j.clml.2021.04.009.

[12] Deepika Kubsad, et al. "Assessment of Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology, Nature, 23 (2019)

infections, obesity, alcohol use, radiation, stress, exposure to heavy metals and pollutants etc. According to the authors the results necessitate further investigation of glyphosate related to breast cancer risks.[13]

Independent reviews have questioned the reliability of many of the industry studies recently relied upon by the European Chemicals Agency (ECHA) to conclude that glyphosate is not carcinogenic.[14] While the ECHA did review a wide range of evidence and concluded that the hazard classification for glyphosate would not change, this review was limited to glyphosate proper and did not evaluate risks of the actual end use products including with formulants and adjuvants. There is a known line of evidence that formulants and adjuvants increase the risks of glyphosate exposure.[15] The European Food Safety Agency (EFSA) in contrast, reviews the risks of the use of glyphosate end-use products and that review is both overdue and forthcoming.
In his study of why IARC and the EPA reached diametrically opposite conclusions on whether glyphosate was a human carcinogen, Charles Benbrook reached these findings:

> 1. The EPA's genotoxicity assessment was primarily based on company-commissioned unpublished Regulatory reports, 99% of which showed glyphosate was negative for genotoxicity. IARC selected mostly peer-reviewed studies of which 70% were positive for genotoxicity or carcinogenicity.
> 2. The EPA's evaluation of glyphosate health effects was largely based on the pure chemical glyphosate, whereas IARC reviewed results of glyphosate-based formulations including the degradation product AMPA (aminomethylphosphonic acid) and the surfactant POEA (polyoxyethylene tallow amine).
> 3. The EPA's evaluation was premised on typical, general dietary exposure and assuming

[13] Duforestel M, Nadaradjane A, Bougras-Cartron G, Briand J, Olivier C, Frenel JS, Vallette FM, Lelièvre SA, Cartron PF. Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner. Front Genet. 2019 Sep 27.
[14]Armen Nerseyan et al. "Evaluation of the cientific quality of studies concerning genotoxic properties of glyphosate"
https://s3.amazonaws.com/s3.sumofus.org/images/Evaluation_scientific_quality_studies_genotoxic_glyphosate.pdf
[15] Defarge N, et al "Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels" Int J Environ Res Public Health. (2016) Feb 26;13(3):264. doi: 10.3390/ijerph13030264; Mesnage R, Antoniou MN. "Ignoring Adjuvant Toxicity Falsifies the Safety Profile of Commercial Pesticides" Front Public Health. 2018 Jan 22;5:361. doi: 10.3389/fpubh.2017.00361; Robin Mesnage, et al, "Insight into the confusion over surfactant co-formulants in glyphosate-based herbicides," Food and Chemical Toxicology, 128, (2019) 137-145 https://doi.org/10.1016/j.fct.2019.03.053; Sheldon Krimsky "glyphosate-based herbicides and public health: making sense of the science" Journal of Agricultural and Environmental Ethics (2022) 35(3) https://doi.org/10.1007/s10806-021-09874-z. Defarge, N. et al. "Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides. Toxicology Reports, (2018) 5, 156–163; Hao, Y. W., et al.. "Adjuvant contributes Roundup's unexpected effects on A549 cells" Environmental Research, 184(109306), 1–8 (2020); Mesnage, R., Clair, E., & Séralini, G.-E. "Roundup® in genetically modified plants: Regulation and toxicity in mammals" In B. Breckling & R. Verhoeven (Eds.), Implications of GM-crop cultivation at large spatial scales. Theorie in der Ökologie16. Frankfort; Peter Lang. et al.. Systematic review of comparative studies assessing the toxicity of pesticide active ingredients and their product formulations. Environmental Research, (2020) 181, 108926.

legal food-crop uses of glyphosate and neglected higher occupational exposures, which IARC considered.[16]

The EPA's carcinogenicity evaluation was also heavily criticized earlier in 2022 by the U.S. Court of Appeals for the Ninth Circuit. On June 17, 2022, the U.S. Court of Appeals for the Ninth Circuit vacated the human health portion of the glyphosate.[17] The Court held that EPA's conclusion was in tension with parts of the agency's own analysis and with the 2005 Guidelines for Carcinogen Risk Assessment ("Cancer Guidelines"), which EPA purported to follow. The panel noted that earlier in the Cancer Paper, EPA had explained that a conclusion regarding the association between glyphosate exposure and risk of non-Hodgkin's lymphoma ("NHL") could not be determined based on the available evidence. In coming to that determination, the Cancer Paper discussed human epidemiological studies showing what could be considered suggestive evidence that glyphosate exposure causes NHL. For example, the Cancer Paper stated that "reported effect estimates across case-control studies and the associated meta-analyses [were] greater than 1," meaning that most studies EPA examined indicated that human exposure to glyphosate is associated with an at least somewhat increased risk of developing NHL.

The Cancer Paper also acknowledged that some epidemiological studies provide evidence of an exposure-response relationship between glyphosate and NHL. One study, for instance, indicated that there was an increased risk of NHL for those with more than ten years of glyphosate exposure. In addition, that same study as well as another indicated that those who are exposed to relatively more glyphosate in a year face a higher risk of NHL. The Court held as a result that EPA's own conclusion from that epidemiological evidence is inconsistent with its ultimate selection of the "not likely" hazard descriptor.[18]

The Court held that EPA's Cancer Paper uses historical-control data selectively and in a manner that is inconsistent with the Cancer Guidelines and only to discount studies that glyphosate may cause tumors. According to the 2016 EPA scientific advisory panel, there were numerous instances in which historical-control data could add weight to tumor findings, but EPA never used the data in that manner. As the scientific advisory panel observed, "[t]o subjectively choose to use historical control incidence data only in situations where" it ultimately undermines tumor results "is to potentially introduce biases." The Court also critiqued the EPA's analysis of tumor incidences in rodents because they were not statistically significant in pairwise comparison tests. Criticizing EPA's approach, "the [SAP] noted that requiring a significant pairwise comparison . . . in addition to a significant trend is neither consistent with the [Cancer Guidelines] nor a conservative approach for public health protection." The Court also found that EPA's disregard of tumor results occurring at high dosages conflicts with the guidelines EPA purports to follow,

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[16] Benbrook, C. M. "How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?" Environmental Sciences Europe, (2019) 31(2), 1–16.
[17] *NRDC v. EPA* https://cdn.ca9.uscourts.gov/datastore/opinions/2022/06/17/20-70787.pdf
[18] *NRDC v EPA*. These meta-analyses—which aggregate and analyze the results from individual studies—quantify the increased risk found across the many case-control studies EPA considered. See Definition: meta- analysis, National Cancer Institute, https://www.cancer.gov/ publications/dictionaries/cancer-terms/def/meta-analysis. The effect estimates from the meta-analyses range from 1.3 to 1.5, indicating that those exposed to glyphosate were 30 to 50 percent more likely to develop NHL.

the Cancer Guidelines do not support disregarding results simply because they are based on exposures that exceed typical human-exposure levels.[19]

The 9th Circuit Court found that the EPA could not reasonably treat its inability to reach a conclusion about NHL risk as consistent with a conclusion that glyphosate is not likely to cause cancer within the meaning of the Cancer Guidelines. The Court concluded that EPA's determination that glyphosate was not likely to be carcinogenic was not supported by substantial evidence. The Court vacated the human-health portion of the EPA's Interim Decision and remanded for further analysis and explanation. This explanation is still outstanding and has yet to be provided by the EPA.[20]

The PMRA used a similar approach to that of the EPA in assessing carcinogenicity in its re-evaluation of glyphosate. This approach is flawed and needs to be revisited prior to granting further glyphosate renewals. The PMRA's 2017 re-evaluation decision frequently refers to the PMRA's collaboration with USEPA on the re-evaluation of glyphosate. For example, the PMRA's overview of the animal study assessment of carcinogenicity potential states that "although, not all available carcinogenicity studies on glyphosate were submitted to the PMRA, reviews, evaluation reports, and committee meeting documents from international regulatory authorities (EFSA and USEPA) for these particular studies were considered by the PMRA.[21] The PMRA appeared to rely on EPA cancer guidelines in assessing the toxicity of glyphosate.[22] The PMRA appears to rely on the conclusions of the EPA assessment and "observed" the scientific advisory panel recommendations from 2016, but did not review al of the cancer studies submitted to the US EPA independently or speak to the flaws in the EPA's analysis identified by the scientific advisory panel.[23]

Other examples that suggest a parallel between the PMRA and USEPA assessment can be found in PMRA's weight-of-evidence analysis conclusion.[24] These examples include the following determinations:

- The statistically significant findings via pairwise comparisons were weighed against the lack of dose-response relationships.

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[19] *Ibid*.
[20] EPA "Glyphosate" (Oct 6 2022) https://www.epa.gov/ingredients-used-pesticide-products/glyphosate "EPA's underlying scientific findings regarding glyphosate, including its finding that glyphosate is not likely to be carcinogenic to humans, remain the same. In accordance with the court's decision, the Agency intends to revisit and better explain its evaluation of the carcinogenic potential of glyphosate and to consider whether to do so for other aspects of its human health analysis."
[21] RVD2017-01, at 20.
[22] RVD2017-01 at 18-21.
[23] RVD2017-01 at 20 para 3 "Although, not all available carcinogenicity studies on glyphosate were submitted to the PMRA, reviews, evaluation reports, and committee meeting documents from international regulatory authorities (EFSA and USEPA) for these particular studies were considered by the PMRA. No evidence of carcinogenicity was identified in any of the rat studies reviewed by the PMRA, or in the additional rat studies reviewed by other regulatory authorities."
[24]RVD2017-01, at 23.

- The statistically significant positive trend was weighed against the lack of consistency across several relevant studies from a total of fourteen long term toxicity/carcinogenicity studies in rodents.
- Incidences fell within valid historical control data from the respective performing laboratories.

The PMRA dismissed tests showing an increase of tumor incidences, writing that "since the adenomas were observed at the limit dose of testing, they were not considered relevant for human health risk assessment."[25] Because the U.S. Appeal Court critiqued similar conclusions in the USEPA's assessment, this supports our view that the PMRA's evaluation of carcinogenicity of glyphosate was not scientifically based.

On genotoxicity the PMRA stated "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"[26] In the 2017 re-evaluation decision the PMRA gave weight to negative genotoxicity studies reviewed by Kier and Kirkland that were later revealed to have been ghost-written by consultants and employees working for the registrant. The PMRA used the same flawed approach of assuming that genotoxic effects are due to cytotoxicity that the EPA used, and which were critiqued by the 9th circuit court. The PMRA's evaluation of genotoxicity is out of date, does not consider newer genotoxicity studies, and does not appear to address the impact of formulants on toxicity and therefore the level of protection provided by the reference doses selected by the PMRA is uncertain.

According to USEPA's Cancer Guidelines, the highest dose "is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity."[27] Just as the USEPA argued that confounding factors may drive positive NHL results, the PMRA states that a number of confounding factors render epidemiological studies inconclusive.[28] Although the PMRA also noted that the association between glyphosate exposure and multiple myeloma required additional follow-up, concerns over their inability to reach a conclusion are left out of the cancer assessment.[29]

In the 2017 re-evaluation document, PMRA finds that the "currently available epidemiology evidence does not support a causal relationship between exposure to glyphosate and cancer outcomes."[30] That decision again draws on reasoning similar to USEPA's, including references to "non-statistically significant" association between glyphosate use and NHL cases, confounding factors, and inability to determine causation due to test inconsistencies and contradictory results.[31] In the re-evaluation, the PMRA sought a "causal" relationship and ignored "gradations" of causality. With these direct parallels between PMRA and USEPA's

[25]RVD2017-01, at 21.
[26] Response to Equiterre Objection (No. 2017-3055) January 11, 2019, p.6.
[27] *NRDC v USEPA*, at 33.
[28] PVRD2015, at 15.
[29] *Ibid*.
[30] RVD2017-01, at 22.
[31]*Ibid*, at 22-23.

analysis, the PMRA's epidemiology assessment should be revisited following the U.S. court decision and incorporating new information.[32]

It is evident that the PMRA relied heavily on the EPA's assessment in the 2015-2017 re-evaluation. This is confirmed in the joint work plan between the EPA and the PMRA as well as in the 2017 re-evaluation decision.[33] The conclusions reached by the PMRA and the EPA appear to be inconsistent with the onus being placed on the registrant under the Canadian *Pest Control Products Act* to establish reasonable certainty that no harm to human health will occur.

Neurodegenerative and reproductive toxicity needs to be revisited

Glyphosate is also increasingly linked to neurodegenerative disorders in humans as it infiltrates the brain.[34] There is a large and growing body of evidence that the gut microbiome alters susceptibility to great number of human diseases, resulting in impaired nervous system function. The weight of the evidence indicates that in addition to cancer and reproductive effects, glyphosate and GBHs have significant adverse effects on the brain and behavior and increase the risk of at least some serious neurological diseases.[35] These same effects are linked to reproductive toxicity including "strong experimental evidence, in animal models and in vitro studies, of glyphosate toxicity in reproduction and development as well as related metabolic and disease consequences. Several of these studies show significant health consequences for mothers, fetuses, and offspring, even several generations after exposure".[36] Another study demonstrates a potential mechanism by which microbiota dysbiosis induced by glyphosate can lead to reproductive toxicity, directly linked to the immune system and inflammatory signalling.[37] Another 2018 study found that > 90% of pregnant women had detectable glyphosate levels in urine and that higher glyphosate urine levels were significantly correlated with shortened gestational lengths.[38]

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[32] Gabriella Andreotti, "Glyphosate Use and Cancer Incidence in the Agricultural Health Study" JNCI: Journal of the National Cancer Institute, 110(5) (2018) 509–516, https://doi.org/10.1093/jnci/djx233

[33] REV20210-02 and RVD2017-01 at p.9.

[34] Winstone, J.K., Pathak, K.V., Winslow, W. et al. "Glyphosate infiltrates the brain and increases pro-inflammatory cytokine TNFα: implications for neurodegenerative disorders" J Neuroinflammation 19, 193 (2022). https://doi.org/10.1186/s12974-022-02544-5; Marino M, Mele E, et al. "Pleiotropic Outcomes of Glyphosate Exposure: From Organ Damage to Effects on Inflammation, Cancer, Reproduction and Development" Int J Mol Sci. 2021 Nov 22;22(22):12606. Torretta, V et al. "Critical Review of the Effects of Glyphosate Exposure to the Environment and Humans through the Food Supply Chain" Sustainability 2018, 10, 950; Najm Alsadat Madani et al "Effects of glyphosate and glyphosate-based herbicides like Roundup™ on the mammalian nervous system: A review," Environmental Research, 214(4) (2022) https://doi.org/10.1016/j.envres.2022.113933 ; Jing-Bo Liuet al "Glyphosate damages blood-testis barrier via NOX1-triggered oxidative stress in rats: Long-term exposure as a potential risk for male reproductive health," Environment International, 159 (2022) 107038, https://doi.org/10.1016/j.envint.2021.107038.

[35] *Ibid*.

[36] Mendez F, et. al. "Effects of Glyphosate Exposure on Reproductive Health: A Systematic Review of Human, Animal and In-Vitro Studies" Exposure and Health. 2021.

[37] Liu JB, et. al. "Glyphosate-induced gut microbiota dysbiosis facilitates male reproductive toxicity in rats" Sci Total Environ. 2021 Sep 16.

[38] Parvez, S., Gerona, R.R., Proctor, C. *et al.* Glyphosate exposure in pregnancy and shortened gestational length: a prospective Indiana birth cohort study. *Environ Health* 17, 23 (2018). https://doi.org/10.1186/s12940-018-0367-0

Endocrine disruption was excluded from the PMRA in the 2017 assessment. Yet the most recent scientific knowledge shows that glyphosate has eight of the ten characteristics specific to endocrine disruptors and that new prospective studies of cohort would be necessary to obtain a more accurate assessment of the real risks incurred by human populations. Current data suggest an association between exposure to glyphosate and the risk of birth defects, miscarriages and reduced fertility.[39]

Exposures need to be reconsidered

International human exposure studies and biomonitoring continue to find high levels of exposure to glyphosate.[40] Conventional water treatment systems currently used for water purification are insufficient to remove traces of contaminants such as herbicides.[41] Canada still lacks any biomonitoring for glyphosate. This should be addressed with analyses of bio-banked urine samples from the Canadian Health Measures survey.[42] Bystander and environmental exposures need to be re-assessed given that the PMRA has not assessed recent evidence of glyphosate long distance drift.[43]

Environmental risk assessment is out of date

The PMRA's 2015-2017 re-evaluation is now out of date as it does not address new evidence of potential risks that raise uncertainty about whether environmental harm will occur.

The line of evidence showing adverse impacts to pollinators and exposure to pollinators has also become more firmly established since 2017.[44] The PMRA continues to lack a toxicity endpoint for milkweed. A robust evaluation of milkweed impacts and the resulting impacts on now-endangered

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[39] Juan P. Muñoz, et al "Glyphosate and the key characteristics of an endocrine disruptor: A review" Chemosphere, 270 (2021) https://doi.org/10.1016/j.chemosphere.2020.128619.

[40] CDC "National Health and Nutrition Examination Survey – Glyphosate" (June 2022) https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSGLYP_H.htm ; Environmental Defence "What's in Your Lunch" (2018) https://environmentaldefence.ca/wp-content/uploads/2018/09/Whats-In-Your-Lunch-Glyphosate-Report-Sept-2018.pdf ; Grau, D., et al. "Quantifiable urine glyphosate levels detected in 99% of the French population, with higher values in men, in younger people, and in farmers" Environ Sci Pollut Res 29, 32882–32893 (2022). https://doi.org/10.1007/s11356-021-18110-0; Gillezeau, C., et al. "The evidence of human exposure to glyphosate: a review" Environ Health 18, 2 (2019). https://doi.org/10.1186/s12940-018-0435-5.

[41] Álvarez Bayona María Angélica, "Occurrence of glyphosate in surface and drinking water sources in Cúcuta, Norte de Santander, and its removal using membrane technology" Frontiers in Environmental Science 10 2022 https://www.frontiersin.org/articles/10.3389/fenvs.2022.941836

[42] US Centers for Disease Control and Prevention (CDC). "National Health and Nutrition Examination Survey. 2013-2014 Data Documentation, Codebook, and Frequencies. Glyphosate (GLYP) - Urine (SSGLYP_H)," June 2022, https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSGLYP_H.htm#References

[43] Maren Kruse-Plaß et. al. "Pesticides and pesticide-related products in ambient air in Germany" Environ Sci Eur (2021) 33:114 https://doi.org/10.1186/s12302-021-00553-4.

[44] Helander M, Lehtonen TK, Saikkonen K, et al. "Field-realistic acute exposure to glyphosate-based herbicide impairs fine-color discrimination in bumblebees" Sci Total Enviro. 2023;857:159298. doi:10.1016/j.scitotenv.2022.159298; Thompson LJ, et al. "Bumblebees can be Exposed to the Herbicide Glyphosate when Foraging" Environ Toxicol Chem. 2022 Oct;41(10):2603-2612. doi: 10.1002/etc.5442. Epub 2022 Aug 29. PMID: 35866464; Anja Weidenmuller et al "glyphosate impairs collective thermoregulation in bublebees" *Science* (2022) 376:6597; James Crall, "Glyphosate impairs bee thermoregulation," Science, 376, 6597, (1051-1052), (2022)./doi/10.1126/science.abq5554

monarch butterflies was considered outside the scope of the 2015-2017 glyphosate re-evaluation.[45] The PMRA must review current published literature on pollinators and milkweed and determine if there is reasonable certainty that no harm will occur. In particular, the PMRA must consider the addition of the migratory monarch butterfly to the IUCN red list this year.[46]

There are also new lines of evidence establishing new ecological harms to freshwater ecosystems arising from glyphosate use.[47] There is also an emerging line of evidence that glyphosate causes indirect environmental harm. Glyphosate adds phosphorus (P) to agricultural landscapes, influencing the accumulation and cycling of P in soil and nearby surface waters. A 2018 study concluded that P inputs from glyphosate use have now reached levels comparable to those from sources for which P regulations were initiated in the past at levels frequently exceeding 20kg per square kilometre in areas planted with glyphosate-resistant crops.[48] We remind the PMRA that "environment" and by extension environmental harm is more than toxicological risk and pertains to the interactions between natural systems. As such, the PMRA must consider the impacts of habitat loss for both freshwater and terrestrial species.

Additionally, new evidence points to the propensity of glyphosate used in forestry to contribute to ecological harm and forest fires.[49] Glyphosate herbicide used in forested areas persists in the environment for years and can prompt morphological changes in perennial flowers that reduce

[45] PMRA Response to Equiterre Objection (No. 2017-3055) January 11, 2019, p.7.
[46] IUCN "Migratory monarch butterfly now on Endangered IUCN Red List" (2022) https://www.iucn.org/press-release/202207/migratory-monarch-butterfly-now-endangered-iucn-red-list
[47] Barbosa da Costa et al. "Resistance, resilience, and functional redundancy of freshwater bacterioplankton facing agricultural stress" by in Molecular Ecology DOI: doi: 10.1111/mec.16100; MP Hébert et al "Widespread agrochemicals differentially affect zooplankton biomass and community structure" *Ecological Applications*. DOI: doi: 10.1002/eap.2423; Fugère V et al. "Community rescue in experimental phytoplankton communities facing severe herbicide pollution" *Nature Ecology & Evolution*. DOI: https://doi.org/10.1038/s41559-020-1134-5.
[48] Hébert, Marie-Pier, et al. "The overlooked impact of rising glyphosate use on phosphorus loading in agricultural watersheds" Front Ecol Environ 17(1) 1540-9295 (2018) https://doi.org/10.1002/fee.1985;
[49] CBC "grooming forests could be making fires worse, researchers warn" (Nov 2019) https://www.cbc.ca/news/canada/british-columbia/forest-fires-glyphosate-1.5366185 ; Daniels, L.D., R.W. Gray and P.J Burton. (2020). **"**Megafires in British Columbia - Urgent need to adapt and improve resilience to wildfire". *In:* Hood, Sharon M.; Drury, Stacy; Steelman, Toddi; and Steffens, Ron, eds. Proceedings of the Fire Continuum – preparing for the future of wildland fire; 2018 May 21-24; Missoula, MT. Proceedings RMRS-P. Fort Collins, CO: U.S. Department of Agriculture, Forest Service, Rocky Mountain Research Station. Online*;* Lisa J. Wood. "The presence of glyphosate in forest plants with different life strategies one year after application" Canadian Journal of Forest Research. 49(6): 586-594. https://doi.org/10.1139/cjfr-2018-0331; Timms, K., Wood, LJ. "Sub-lethal glyphosate disrupts photosynthetic efficiency and leaf morphology in fruit-producing plants, red raspberry (Rubus idaeus) and highbush cranberry (Viburnum edule)" Global Ecology and Conservation (2020) https://doi.org/10.1016/j.gecco.2020.e01319 2351-9894; Golt, AR, Wood LJ. "Glyphosate-based herbicides alter the reproductive morphology of Rosa acicularis (prickly rose)" Frontiers in Plant Science – Functional Plant Ecology. Manuscript Accepted, May 24, 2021. Manuscript ID #698202; Botten, N. Wood LJ. "Glyphosate remains in forest plant tissues for a decade or more" Forest Ecology and Management 493 (1). doi.org/10.1016/j.foreco.2021.119259; Briere, B., Wood, LJ., Kirby, B., Botten, N. "Sensitivity of non-target annual plants to glyphosate-based herbicide, according to growth form" (2020) Canadian Journal of Pesticides and Pesticide Management. doi:10.34195/can.j.ppm.2020.02.002.

their fertility and may make them less attractive to pollinators.[50] The PMRA has not assessed the impacts of glyphosate forestry uses on Indigenous rights.

Incident reports

The PMRA must also consider new incident reports which have been submitted since 2017 and must properly investigate the causes of the incidents. The public registry shows that there are more than 50 such incident reports, many of which have apparently not been investigated by the PMRA.

Intensity of use data

The PMRA is lacking data on glyphosate food residues relevant to Canadian use patterns and lacks intensity of use data addressing Canada-specific use intensity increases. A comprehensive water monitoring program for glyphosate is lacking. The PMRA needs to require the submission of this data.

Weight of evidence

We acknowledge that the PMRA takes a weight of evidence approach to the review of new research on potential health and environmental impacts. However, the application of the weight of evidence approach must be complete in that it considers relevant evidence. It must also be consistent with the statutory standard of reasonable certainty that no harm will occur in the PCPA. Specifically, in assessing the weight of evidence the question that the PMRA is statutorily charged with is whether the weight of evidence establishes reasonable certainty that no harm will occur.

In this respect the 2021 Framework for Risk Assessment and Risk Management of Pest Control Products is problematic. For example, on page 8, the *Framework* states that "the outcome of the animal studies together with mechanistic considerations are used in a weight-of-evidence approach to decide if a pesticide is likely to pose a cancer hazard." This approach asks whether there is a scientific likelihood of harm, or effectively proof of hazard, rather than reasonable certainty of no harm. This distinction can become significant - for example where evidence is inconsistent or incomplete. Instead, the PMRA should assess the weight of evidence to determine whether there is reasonable certainty of no harm in respect of both health and environmental risks at both the hazard definition and exposure stages of risk assessment. Even where new evidence falls short of establishing that harm is "likely" it may cause a loss of reasonable certainty. The onus is on the registrant to provide sufficient, complete information that is enough to establish reasonable certainty that no harm will occur. Such conclusions must e informed, and cannot be reached merely on the basis of lack of evidence of harm, or in the absence of sufficient evidence.

[50] Golt, AR, Wood LJ. "Glyphosate-based herbicides alter the reproductive morphology of Rosa acicularis (prickly rose)" Frontiers in Plant Science – Functional Plant Ecology. Manuscript Accepted, May 24, 2021. Manuscript ID #698202

Conclusion

In our submission the PMRA must not renew existing glyphosate registrations without considering the above information. The PMRA must determine that it has reasonable certainty that no harm would occur. If the registrant has failed to provide additional research that resolves the concerns raised in the published literature and incident reports prior to seeking renewal then the registrant has not met its obligations under sections 6, 8 and 16 of the *Pest Control Products Regulations* nor under section 7 of the *Pest Control Products Act* and the PMRA must not renew the registrations. The information above points to new or more clearly established risks that the PMRA has not assessed as well as the potential for a lower toxicology reference values and new information on increased exposures.

Sincerely,

Laura Bowman
Staff Lawyer

cc: Minister of Health hcminister.ministresc@hc-sc.gc.ca
PMRA renewals team pmra.renewal-renouvellement.arla@hc-sc.gc.ca