Comments on Proposed Maximum Residue Limit

PMRL 2021-10, Glyphosate

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Introduction

On May 6, 2021, the Pest Management Regulatory Agency (**PMRA**) issued a Summary Report on "Proposed Maximum Residue Limit PMRL 2021-10 Glyphosate" (the **Proposal**). It indicated that under the authority of the Pest Control Products Act (**PCPA**), it was proposing to establish maximum residue limits (**MRLs**) for glyphosate on various commodities "to permit the import and sale of foods containing such residues…". It invited written comments from the public for 75 days.

Table 1 of the Summary Report spoke to the establishment of new recommended MRLs, including:

- 15 parts per million (ppm) for "all commodities of crop subgroup 6C, except soybeans, dry lentils, dry field peas and dry pigeon peas", to replace the previous MRL of 4 ppm;
- 10 ppm for dry field peas and dry pigeon peas, to replace the previous MRL of 5 ppm; and
- 10 ppm for lentils because they are considered as peas, to replace the previous MRL of 4 ppm.

It indicated that glyphosate on succulent (not dried) peas and beans of crop subgoups 6A and 6B would be covered by the default MRL of 0.1 ppm.

These MRLs were proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage. Table 2 provided a comparison of the "MRLs proposed for glyphosate in Canada" with American tolerances and Codex MRLs.

An "Update" was issued and indicated the consultation was extended until September 3, 2021. The Update indicated that the "Proposed MRLs for consultation" included Canadian and Codex MRLs, and listed both "Current" Canadian and Codex MRLs and "Proposed" Canadian and Codex MRLs, and also stated "[u]p to date MRLs are necessary to ensure domestic and imported foods meet Canadian food safety standards".

It is evident from the above that the Summary Report was describing a proposal to increase the MRLs for glyphosate on the commodities in the listed crop groupings. These commodities include foods that are both grown domestically in Canada and imported into Canada.

PMRA produced "Evaluation Report for Category B, Subcategory 5.0 Application, Application No. 2019-1027 New Maximum Residue Limits for Previous Assessed Technical Grade Active Ingredient (PMRA Document Number 3161627)" (**Evaluation Report**). The Evaluation Report was for a "Category B, Subcategory 5" application , which is an application for "New import MRL for a previously assessed TGAI [Technical Grade Active Ingredient]", according to Regulatory Directive 2003-1 Guidance on Selecting the Correct Category for Pest Control Product Submissions (p.13).

The Evaluation Report purports to be in support of MRLs for residues "in/on imported dry peas and dry beans from crop subgroup 6C", but it provides a "recommendation for new and/or updated maximum residue limits (MRLs) for glyphosate in/on dry peas, dry beans and tree nuts", not just for glyphosate on imported crops. The recommendation was "based upon field trial data, as well as the guidance provided in the OECD Calculator".

In the Evaluation Report, PMRA spoke to "Health Assessments" in one section, and in that section indicated that it had reviewed field trial data from field trials in Canada and the US for dry peas and dry beans and tree nuts, and updated the dietary exposure assessment. It stated that toxicology and occupational exposure assessments were not required.

We provide comments below on the health risk assessment of PMRA used as the basis for the increases (**Increases)** in the MRLs outlined in the Summary Report. As indicated above, it is apparent from the Summary Report and the Evaluation Report that the proposal to increase MRLs on dry beans, dry lentils and dry peas (the **Proposed MRLs**), as a proposal for MRLs on specific crop subgroups, is a proposal to increase MRLs that affects both domestic and imported crops. These comments make that assumption and are written from that perspective.

Footnotes can be found at the bottom of the applicable pages. References that are endnotes are found at the end of these comments.

PMRA Does Not Have Jurisdiction to Increase Domestic MRLs

The PMRA does not have jurisdiction under the PCPA to increase the glyphosate MRLs under the Proposal. The jurisdiction would come from section 9 or 10 of the PCPA, but both of those are not triggered in the instant situation.

Sections 9, 10 and 11 of the PCPA concern Maximum Residue Limits.

Section 9 states:

> **Specification at time of registration decision**
> **9** When making a decision regarding the registration of a pest control product, the Minister shall, if necessary, specify any maximum residue limits for the product or for its components or derivatives that the Minister considers appropriate in the circumstances.

Section 9 concerns specification of an MRL at the time the Minister (PMRA) is making a registration decision. The Proposal came about "in response to an application from a registrant to align MRLs with those proposed by the Food and Agriculture Organization and World Health Organization's Codex Alimentarius", according to the Update, not because the PMRA was making a registration decision on glyphosate. Section 9 is clear that it applies in the case of a "decision regarding registration", not an amendment to such a registration decision, which is contemplated and explicit elsewhere in the PCPA, and so it is not applicable.

Section 10 states:

> **Specification for unregistered products and uses**
> **10 (1)** The Minister may specify maximum residue limits for an unregistered pest control product or its components or derivatives, or for a registered pest control product or its components or derivatives with respect to a use that is not provided for by its registration, whether or not an application under subsection (2) is made for that purpose.

Section 10 concerns, first, specification of an MRL for an unregistered pest control product, and second, an application for a new use that is not provided for in the registration. Neither is applicable. First, glyphosate is already a registered product, and no new use is being proposed. Second, the categorization of the Evaluation Report as a report to establish MRLs for imported commodities

represents an import scenario, not a new use scenario. In Regulatory Directive 2003-1, criteria are provided for submissions concerning new uses, and the "Category B, Subcategory 5" application of the Evaluation, which is an application for "New import MRL for a previously assessed TGAI [Technical Grade Active Ingredient]", is not a new use scenario.

The wording of Section 11(1) specifically references the specification of MRLs under sections 9 and 10, and the wording of Section 11(2) references the evaluation of the risks of MRLs undertaken under Section 11(1), which is tied to the specification of MRLs under Sections 9 and 10. The full Section 11 states:

> **Health risks to be considered acceptable**
> **11 (1)** The health risks associated with maximum residue limits specified by the Minister under sections 9 and 10 must be considered to be acceptable by the Minister.
>
> **Relevant factors**
> **(2)** If a decision referred to in paragraph 28(1)(a) or (b) is being made or has been made in relation to a pest control product, the Minister shall, in evaluating and determining whether the health risks associated with maximum residue limits for that pest control product or its components or derivatives are acceptable under subsection (1),
> (a) among other relevant factors, consider available information on
> (i) aggregate exposure to the pest control product, namely dietary exposure and exposure from other non-occupational sources, including drinking water and use in and around homes and schools,
> (ii) cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity, and
> (iii) the different sensitivities to pest control products of major identifiable subgroups, including pregnant women, infants, children, women and seniors; and
> (b) in the case of a threshold effect, apply a margin of safety that is ten times greater than the margin of safety that would otherwise be applicable under subparagraph 7(7)(b)(ii) or 19(2)(b)(ii) in respect of that threshold effect, to take into account potential pre and post-natal toxicity and completeness of the data with respect to the exposure of, and toxicity to, infants and children, unless, on the basis of reliable scientific data, the Minister has determined that a different margin of safety would be appropriate.

The reference in Section 11(2) to a registration decision "having been made" is what may lead to an incorrect interpretation that Section 11(2) allows for setting of MRLs at a time that is not the time of an application for registration or a new use. But this is not the case; the wording of a decision "having been made" would apply in the context of an application for a new use to an existing registration. It would not apply in the case when a registrant just asks for an increased MRL.

Even if the PMRA does have jurisdiction to propose an increase to MRLs at this time, it would be prudent to not. The reason is that much of the science and scientific arguments relied upon by PMRA in its Health Assessment are based on the science and rationale set out in Proposed Re-evaluation Decision PRVD 2015-01 and Re-evaluation Decision RVD2017-01 on Glyphosate.

The final registration decision, RVD2017-01, was the subject of a recent court case at the Federal Court of Appeal concerning objections made under the notice of objection section of the PCPA, section 35. The Federal Court of Appeal remitted the objections back to the PMRA, and the possibility exists that PMRA may establish an independent review panel. An independent review panel could recommend confirmation, amendment or reversal of the final registration decision, meaning the final registration decision in its current form may not stand. Changes could call into question not only the science from PRVD2015-01 and RVD2017-01, but also any such science relied upon by PMRA for the Proposal.

This jurisdiction argument aside, the rest of these comments are written from the perspective that PMRA does have jurisdiction under section 11 of the PCPA to propose increases to MRLs.

Concerns with the Establishment of the Proposed MRLs

Proposed Values are Too High, Not Protective and Do Not Reflect Actual Field Trial Data Reported

The numerical values for the Proposal's increases in MRLs for dry pea seed, dry lentil seed and dry bean seed put forward in the Proposal by PMRA came from the Extra Joint FAO/WHO Meeting (the **Extra JMPR Meeting**) on Pesticide Residues held in Ottawa/Gatineau in May 2019. The resulting 2019 Report Pesticide Residues in Food (the **JMPR Report**) discusses Glyphosate at pages 79-81. It therein discusses field trail data on lentils, dry peas and beans, and this data is the data summarized by PMRA in Table A-1 of the Evaluation Report.

The summary in the Evaluation Report provides information on the Lowest Average Field Trial (**LAFT**) and the Highest Average Field Trial (**HAFT**), and sets out a "Recommended MRL", but does not provide any explanation or analysis regarding the calculation of the Recommended MRL.

The JMPR Report also discusses *Dry Beans, except soya bean,* and therein discusses field trial results on dry beans. The results were:

Residue Field Trial on Crops	Highest trial residue reported	Average or trial residues reported	STMR	Previous MRL (mg/kg)	New estimated MRL/ STMR (mg/kg)
a) 13 dry bean trials	10 mg/kg. The next highest is 2.6 mg/kg	1.35 mg/kg. Discarding the 10 mg/kg, the average is 0.63 mg/kg	0.32 mg/kg	2	15/ 0.32

The JMPR Report also discusses *Dry Peas, subgroup of,* and therein discusses field trial results on lentils and dry peas, and then combined. A summary is below:

Residue Field Trial on Crops	Highest trial residue reported	Average of trial residues reported	Supervised Trials Median Residue (STMR)	Previous MRL (mg/kg)	New estimated MRL/ STMR (mg/kg)
a) 11 lentil trials	6.4 mg/kg	2.25 mg/kg		5	10/1.7
b) 5 dry pea trials from 1998	4.2 mg/kg	2.034 mg/kg		5	10/1.7
c) Combined	6.3 mg/kg	2.18 mg/kg	1.7 mg/kg	5	10/1.7

Based on the above, the Extra JMPR meeting "estimated a maximum residue level for the subgroup of dry peas at 10 mg/kg …and a Supervised Trial Median Residue (**STMR**) of 1.7 mg/kg, and withdrew the previous maximum residue level recommendations for pea dry and lentil of 5 mg/kg".

Based on the above, "The Meeting noted that dry bean is the representative commodity for the dry beans subgroups, and "estimated a maximum residue level for of 15 mg/kg and a STMR of 0.32 mg/kg for glyphosate for the dry beans subgroup (except soya bean). The Meeting withdrew its previous recommendations of 2 mg/kg".

The estimations of MRLs at high values of 10 mg/kg and 15 mg/kg by the JMPR Meeting are not rationally or scientifically connected to the actual field trial data as reported in the JMPR Report. Although the MRLs are described as "estimates", as reported they do not appear to be true estimates, because an "estimate" is an approximate judgement or calculation that would be based on the actual findings. Merriam Webster defines it as: "a numerical value obtained from a statistical sample."

The findings as reported do not support such high values. By way of example:

- In the case of lentils, the recommended/ estimated MRL of 10 mg/kg is 1.56 times higher than the highest residue reported for the lentil trials of 6.4 mg/kg, and 4.4 times higher than the average of the reported trial residues of 2.25 mg/kg.
- In the case of dry peas, the recommended/ estimated MRL of 10 mg/lg is 2.38 times higher than the highest residue reported for the dry pea trials of 4.2 mg/kg, and 4.92 times higher than the average of the reported trial residues of 2.034 mg/kg.
- In the case of dry beans, the recommended/ estimated MRL of 15 mg/kg is 1.5 times higher than the highest residue reported for the dry beans trials of 10 mg/kg, and 11.11 times higher than the average of the reported trial residues of 1.35 mg/kg. If the high reported trial value of 10 mg/kg is discarded as an outlier, the estimated/recommended MRL of 15 is 23 times higher than the average of the reported trial residues of 0.63mg/kg.
- The recommended/estimated MRL for lentils and dry peas combined of 10 mg/kg is 5.88 times higher than the Supervised Trial Median Residue of 1.7 mg/kg.
- The recommended/estimated MRL for dry beans of 15 mg/kg is 47 times higher than the Supervised Trial Median Residue of 0.32 mg/kg.

OECD MRL Calculator Overestimates MRLs

It appears the basis for the high values is statistics, not science. PMRA relies on the OECD Calculator to establish MRLs. The OECD MRL Calculator Statistical White Paper (ENV/JM/MONO(2011)3 discusses different possible statistical approaches to datasets, and provides a justification for the OECD's selection of a base method of "Mean + 4*SD". However, in its own concluding words (p. 41), OECD explains that this "produced much more conservative methods and **increased overestimations**" for small datasets. It understands that for small datasets the MRL proposal is "above the HR [highest residue] of the parent [actual field trial] dataset much more frequently than below" (p. 25).

PMRA attempts to justify its use of a statistical method that allows for "increased estimations". In its "Response to comments received on PMRL consultations for proposed new maximum residue limits of various pesticides (PMRL2021-15 to PMRL2021-30)", it states (in the section on "Calculating MRLs"):

> "The [OECD] calculator compares the lowest residue with the highest residue; the larger that range is, the greater the difference present in the data. This difference is taken into account when computing the MRL and **may lead, in some cases, to MRL proposals significantly greater than the highest residue**."

Such an approach runs counter to PMRA/ Health Canada statements, policy and the primary purpose of the PCPA, which is to protect Canadians from the risks of pesticides. By allowing MRL values that are overestimations of amounts that occur in field trials, where the product is applied according to label directions, PMRA is setting Canadians up for exposure at levels that are not justified by established use patterns. It is permitting levels of pesticides on food in Canada that are above those allowed by the label directions in Canada.

That the OECD approach runs counter to Health Canada statements is evident from statements of the PMRA on the issue. The Annual Report of PMRA indicates MRLs are "the maximum amount of residue that is expected to remain on food products when a pesticide is used according to label directions" (PMRA, Annual Report 2020-2021, p. 7) The 10 and 15 mg/kg values are much higher than the actual findings for glyphosate in the field trials.

A similar statement is found on Health Canada's webpage "Maximum Residue Limits for Pesticides", which was up to date as of March 23, 2022. Health Canada in the statement consider MRLs to be representative of actual levels found on the crops. It speaks to the "maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions":

> "As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) and is regulated under the *Pest Control Products Act*. (emphasis added)

The "overestimated" MRLs set by the statistical approach of the OECD Calculator provide results that greatly exceed the amount of residues that are expected to remain on food products when the pesticide is used according to the label directions. As shown in the Proposal (and as is borne out in the field trial reports themselves), the Proposed MRLs greatly exceed the residues found in the field trials.

The OECD statistical approach is also not consistent with guidelines of the PMRA. Section 11 of PMRA's Residue Chemistry Guidelines (Regulatory Directive - Dir98-02) concerns the scientific data requirements for MRLs that the petitioner (registrant) is expected to provide to PMRA. These Guidelines contemplate the setting of MRLs based on the results of actual field trial data (not statistical extrapolation), as is evident from the following wording in Sections 11.2.1 and 11.3 (pp. 11-2,3):

> "11.2.1 Determining the maximum residue level (MRL)
> To obtain a MRL, the petitioner proposes a MRL level, based on residue field trial data, that reflects the maximum residue that may occur under worst case conditions, i.e., maximum per season rate and minimum preharvest interval (PHI), as a result of the proposed use of the pesticide.
>
> 11.3 Proposed MRLs
> MRLs should be proposed in terms that best represent the ROC on the raw agricultural commodity (RAC), whether it be the parent pesticide, altered forms of it, or both. The proposed MRL should not be based on an average residue value but should be large enough to include any residue values that could be reasonably expected, based on the available data.
>
> The MRL should not be larger than is needed for the proposed use although some limited accommodation to this rule may be necessary in the interest of avoiding an inordinate multiplicity of MRL levels for a single pesticide on a number of different crops.

Concerns with the Field Trials Results

The references provided at the end of the Evaluation Report are reports on the actual field trials (the **Field Trials)** used to support the Proposed MRLs for beans, lentils and peas. The are identified with PMRA Document Numbers as follows:

- the study provided on "Dried Shelled Beans" was PMRA Document Number 2971197 from 2002; and
- the studies provided on "Pea (Dry)" were PRMA Document Numbers 2971191 and [2]971192 from 2005; and 3111910, 3127654 through 312758 from 1999;
- the studies provided on "Lentils" were PMRA Document No. 2971199 from 2018; and PMRA Document Number 3111910, the related 2020 Deficiency Response.

There are various concerns with the reports on the Field Trials (the **Field Trial Reports**) , and the fact that they serve as the basis for the Proposed MRLs.

No Correction for Moisture Content (all)

First, the residue values set out in the Field Trial Reports on Pea(Dry), Lentils and Dried Shelled Bean were all not corrected for moisture content. This means that the residue values were measured at the time when the legumes were harvested and had moisture in them, rather than "dried". Once the legumes dry, the ppm value would increase on a weight ppm basis. This means the residues are more concentrated in the dried vs. the freshly harvested legumes, and values on a ppm basis for dried legumes will be higher than those reported in the Field Trial studies on harvested legumes.

Not Applied in accordance with 30% Moisture Content Label Direction (Lentils and Peas)

Second, the legitimacy of the Field Trials forming the basis for the Proposed MRLs rests on the premise that the pesticide product was applied in the Field Trials according to the label directions. The dietary

exposure assessments (**DEA**) used for the for the Proposal was prepared by or for Monsanto Canada ULC on September 3, 2020 (the **Monsanto DEA**). As stated in the Monsanto DEA, the label requires application when the seed moisture content is 30% or less.

In the Lentil Field Trials, there is no evidence that the pesticide product was applied according to the required label direction, because the moisture content at the time of application was not measured or recorded. When PNRA raised this to Bayer in an April 28, 2020 Deficiency Letter, Bayer confirmed:

> "The percent moisture content values were not measured In the lentil seeds at the time of pre-harvest application for any of the trials".

The Field Trial Reports did present information on the "growth stage" of the crop at the time of product application, generally in terms of the "BBCH" scale. However, as will be discussed, labels do not speak to or require application at a particular growth stage or stage on the BBCH scale, so this does not alleviate the concern.

In the Pea (Dry) Field Trial Reports there is similarly no indication anywhere that the moisture content of the seed was a factor. The focus was on when the plant was "physiologically mature".

Decline Studies show Increases (Beans, Peas, amended with Lentils)

Decline studies are used to establish a relationship between the time of harvest, relative to the time of application, and the amount of residues found on the crop. PMRA indicates, in its November 28, 2003 *Science Policy Note: Guidance for Refining Anticipated Residue Estimates for Use in Acute Dietary Probabilistic Risk Assessment* that the relationship is not necessarily linear, and that decline studies allow PMRA to improve its exposure estimate by incorporating the full range of preharvest intervals:

> "**3. Residue decline studies**
>
> Similar to data from "bridging studies", residue decline data refer to data that can be used to establish a relationship between residue levels at the time of application (or at the label PHI) and residue levels at the range of typical harvest times. These studies recognize that not all crops are harvested at the labeled minimum PHI and are used to establish the relationship between the time of harvest (relative to the last pesticide application) and the level or amount of residues found on the commodity. Because pesticides degrade and dissipate at different rates over time, it cannot be assumed that this relationship is linear, e.g., that doubling the PHI would result in half the residue. In a residue decline study, samples from a single field trial are collected at multiple PHIs and analyzed to determine rates of residue dissipation. A minimum of three intervals is recommended, although at least five are preferable. This information, together with use-related information on what fraction of the crop is harvested at each interval, would permit the Agency to refine its estimates of exposure by incorporating the full range of PHIs. This kind of information is most useful when there are large differences between the minimum labelled and typical PHIs and when these pesticidal compounds are relatively short-lived.

In the Bean Field Trial decline studies, the majority of the actual findings showed an increase, rather than a decline, in residues for preharvest days 13 and day 20. The average residues for preharvest days 13 and 20 were more than three times those found for preharvest day 7. This means that the actual Field Trial results showed high residue levels for a point in time that is one-day short of the longest preharvest interval permitted in Canada (14 days).

With respect to the Peas (Dry) decline studies, the Field Trials were conducted at two locations. At one location the average residues slightly decreased from the value at 7 days preharvest to the value at 14 days preharvest and then increased at the 21 days preharvest value to just less than the 7 day value. The maximum non-averaged actual value was at day 21 PHI. However, at the second location, the average values significantly increased rather than declined; by a factor of almost 1.5 from day 7 to day 13, and by a factor of almost 1.6 from day 7 to day 21. This means that, for that location, the residues of the product in the crop were actually increasing the longer the product was in the crop. The maximum non-averaged value for the second location was also at day 21 PHI, although it was close to the non-averaged actual value at day 14 PHI.

With respect to Lentil decline studies, is it appears the original 2011 finding contained information on a "decline" field trial, but that the Field Trial Report was amended in 2018 apparently, in part, to delete the finding of the decline trial. Reference to the report containing information on the "decline" of residues can be found in the "Purposes" sections of PMRA Document No. 2971199, where the purpose of the study is described as "to determine the magnitude and decline of residues of glyphosate and AMPA in lentil seed following one preemergence and one preharvest foliar broadcast application of RoundUp WeatherMax Herbicide to lentils." The amendment as presented in the final Field Trial Report served to include information on the application date of 7 days preharvest, with no mention of testing at decline dates, which generally are at 14 and 21 days.

It is evident from the above that, overall, the residues of glyphosate in the tested crops increased, rather than decreased, over time. However neither the Monsanto DEA or the JMPR Report noted this fact, and PMRA did not see its way to use the results of the decline studies to "improve its exposure estimates". The implication of the decline studies is that residues levels of glyphosate in the subject legumes increase after the PHI of 7, meaning that if the crop is harvested after day 7, the residue levels are likely higher than the 7 day preharvest residue values relied upon by PMRA in setting MRLs. The preharvest interval in Canada is 7 to 14 days, so it is likely that crops will be harvested after day 7.

In other words, the residues increase after day 7, and this has not been incorporated into the exposure estimates. Canadians cannot rely on the dietary exposure assessment to be protective because it likely underestimates the exposure of Canadians to magnitudes of glyphosate in their food.

Scientific Rationale for the Increases

An increase in residue levels over the timeframe after spraying is consistent with the systemic nature of glyphosate. Because glyphosate is systemic, it is continually moving in the system of the plant to the growing points. The growing points in the later stages of plant growth are the seeds. So if glyphosate is applied at a point when a plant is moving nutrients and fluids to the seed from all the points of contact of the herbicide to the plant, the plant, for so long as it is still alive, will move the herbicide from these contact points to the growing seed, and the residues in the seed will continue to accumulate over the time frame until senescence. Glyphosate is sprayed on the entire plant, not just the seed area, so such continuous translocation from contact points is to be expected.

This tendency of the plant that causes it to continuously translocate glyphosate to the seed causes residue levels to accumulate at greater concentrations in the seed over the time frame from spraying until harvest, if it is the case that the plant is still at that stage still growing seeds and translocating fluids to those seed.

Plants have two different types of growth habits: determinate, and indeterminate. In a "determinate" plant, the plant stops producing, growing and filling seed at a certain stage: such growth "terminates". And so if glyphosate is applied after that stage, glyphosate in theory won't translocate to the seed in high levels because the plant is no longer moving fluids and nutrients to the seed.

However, with "indeterminate" plants, the activity of translocating glyphosate to the seed does not decline, at least not until the "senescence", or dying, stages of plant growth (which often occurs with frost). The reason is that the plant does not stop producing, growing and filling seed at a certain stage. An indeterminate plant is continuously growing seeds, and so is continuously moving glyphosate that has been sprayed to these seeds.

The scientific literature provides evidence of the translocation of glyphosate to seeds and accumulation in seeds, and concerns with accumulation in indeterminate plants. The studies generally are trying to identify the stage of physiological maturity or level of seed moisture content that is appropriate for spraying so as to avoid exceeding the MRLs in place by other countries for the crop.

One example is the study, McNaughton, K. et al. Effect of application timing of glyphosate and saflufenacil as desiccants in dry edible bean (Phaseolus vulgaris L.) Can. J. Plant Sci. (2015) 95: 369375 doi:10.4141/CJPS-2014-157. Therein the authors state:

> "Producers sometimes find it difficult to identify the proper timing for desiccant application. Weather conditions and the indeterminate nature of the crop make it probable that while the majority of the field has reached the appropriate maturity for desiccant application, certain areas within a field may be immature and the desiccant may be applied too early." (p.370)

A second example is Zhang, T. et al. Early Application of Harvest Aid Herbicides Adversely Affects Lentil. Agronomy Journal, Volume 109, Issue I 2017: 239. The authors state:

> "The recommended application timing is typically when the crop is at or below 30% seed moisture content (Saskatchewan Ministry of Agriculture, 2016). However, if glyphosate is applied to crops that have not reached physiological maturity, the herbicide may be translocated to developing seeds, resulting in seeds levels exceeding MRLs (Cessna et al, 1994, 2000, 2002)." (p.239-240)
>
> "At early seed development stages, seeds are major sucrose sinks and glyphosate will translocate to those developing seeds. As the crop matures, the demand for sucrose from these sinks declines and less glyphosate is translocating to the developing seeds, resulting in [comparatively] reduced residues (Zhang et al. 2016)."
>
> The thesis written by Zhang T. also explains:
> "Since glyphosate is translocated via phloem, it can move throughout the plant and tends to accumulate in seeds if glyphosate is applied at later crop growth stages (Cessna et al., 1994; Wigfield et al., 1994; Cessna et al., 2000; Cessna et al., 2002).[1]

[1] Cessna, A. J., Darwent, A. L., Kirkland, K. J., Townley-Smith, L., Harker, K. N., & Lefkovitch, L. P. (1994). Residues of glyphosate and its metabolite AMPA in wheat seed and foliage following preharvest applications. *Canadian Journal of Plant Science*, *74*(3), 653-661;

The scientific literature also shows that translocation continues after spraying, by up to 10 to 15 days. By way of example. The authors of the study M.O.Assis et al, "Pre-Harvest Desiccation in Productivity and Physiological Quality of Cowpea Seeds" Article Planta daninha 37(2019) https://doi.org/10.1590/S0100-83582019370100014 state:

> "…[G]glyphosate is a systemic desiccant whose final effect takes 10 to 15 days after the application, without interrupting immediately the transfer of dry matter to the seed, as it happens with the other evaluated herbicides, that have contact action, but with a faster effect, preventing the seed from continuing to accumulate dry matter (Marcos Filho, 2015).
>
> As discussed earlier, the longer interval between the application and the effect of glyphosate contributes so that the seeds do not immediately interrupt the dry matter transfer during the maturation process,….(Marcos Filho, 2015)."

Uses Averages and "Averaging Down" the Results

The Field Trials in certain instances found high actual levels of residues, but the reports tempered them by "averaging" the findings. In some instances, the actual explanation provided for conducting additional trials was because the original findings were too high! By way of example, results from the decline study on Beans actually showed very high individual residue levels at both day 13 and 20, but these were "averaged down" by taking additional samples. The reason provided in the field trial was:

> "Samples were reanalyzed after the first analysis gave glyphosate residue values that were unexpectedly high" (emphasis added)."

Such "averaging down" because of unexpected values cannot be scientifically justified.

The data from the Field Trials as reported in the JMPR Report is skewed toward lower values. The predominance of lower values is underlined by the fact that the median values, reported as the STMR, are very low (1.7 mg/kg (ie. ppm) for dry peas, and 0.32 mg/kg (ie. ppm) for dry beans).

PMRA in the Summary Report Table A1 provided information on the lowest average field trial residue (**LAFT**) and the highest average field trial residues (**HAFT**), but provided no reason or scientific basis for such reporting. The use of the "average" value of HAFT is not scientifically appropriate because it inflates the importance of the small number of higher measures. However, the LAFT and the HAFT are the numbers called for the OECD Calculator for inputting into the OECD MRL calculation, which appears to be why PMRA reports them. As set out in OECD Guidance Document on Crop Field Trials, second edition (para. 100): "It has been determined that the mean or average residue value, when replicate sample data have been generated per field site, should be used in the calculation process".

Wigfield, Y. Y., Deneault, F., & Fillion, J. (1994). Residues of glyphosate and its principle metabolite in certain cereals, oilseeds, and pulses grown in Canada, 1990–1992. *Bulletin of Environmental Contamination and Toxicology*, *53*(4), 543-547;

Cessna, A. J., Darwent, A. L., Townley-Smith, L., Harker, K. N., & Kirkland, K. J. (2000). Residues of glyphosate and its metabolite AMPA in canola seed following preharvest applications. *Canadian Journal of Plant Science*, *80*(2), 425-431;

Cessna, A. J., Darwent, A. L., Townley-Smith, L., Harker, K. N., & Kirkland, K. (2002). Residues of glyphosate and its metabolite AMPA in field pea, barley and flax seed following preharvest applications. *Canadian Journal of Plant Science*, *82*(2), 485-489.

Concerns with Using the JMPR Analysis and Field Trial Results for Canadian MRLs

JMPR incorporated the results of the Field Trials for Dry Peas, Lentils and Dried Shelled Beans into the JMPR Report discussion on glyphosate (at p.80). This JMPR Report provided the "estimates" for the MRLs for "Dry beans, except soya bean" and "Dry peas, subgroup of" that are the 10 ppm and 15 ppm values for the Proposed MRLS proposed by PMRA in the Summary Report for the commodities PMRA describes as "Dry pea seed", "Dry lentil seed" and "Dry bean seed".

The Monsanto DEA on p. 15 sets out the glyphosate data used to determine the updated and new MRLs proposed, and indicated the Canadian MRLs for dry beans, lentils and peas of 4, 4, and 5 ppm respectively will be withdrawn and replaced by the revised MRLs of 15, 10 and 10 ppm respectively.

Beans, dry.

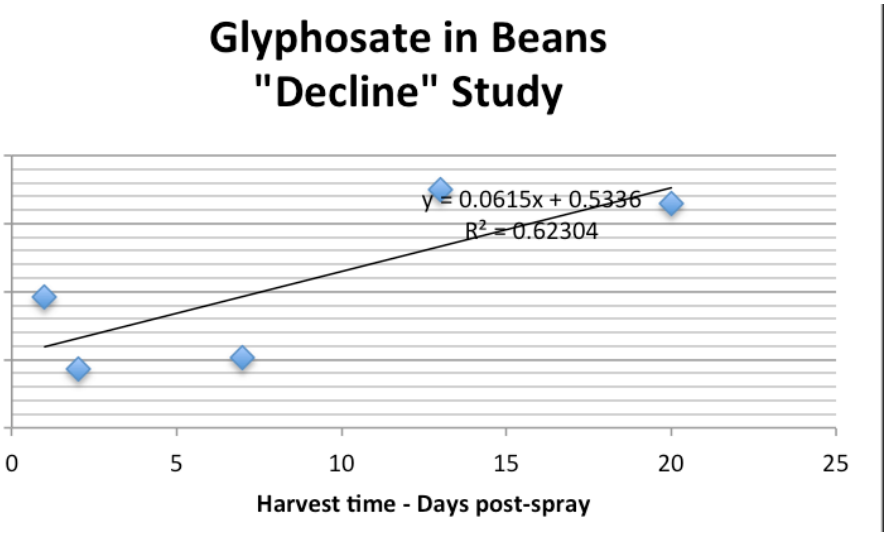
With respect to "Beans, dry", the Monsanto DEA (p.15) indicates results from the US bean field trials were used to determine the recommended MRL 0f 15 ppm. The Monsanto DEA sets out application rates, and indicates that glyphosate is currently registered in Canada for preplant, in-crop spot treatment and preharvest use at rates of **0.9** to 4.32 kg a.e./ha…. and a preharvest interval of **7-14** days. With respect to preharvest use, the 0.9 kg a.e./ha rate and a preharvest interval of 7-14 days is consistent with the application rate for preharvest use stated in PRVD2015-01 p. 99 of Appendix V:

> "The data support a maximum seasonal rate of 6.2 kg a.e./ha in pre-emergent applications and 0.9 kg a.e./ha in pre-harvest applications for forage crops (PHI of 3-7 days) and all other crops (PHI of 7-14 days)".

To the extent the Proposed MRLS will apply to domestic crops , a concern arises because the preharvest application rate used in the bean Field Trial (PMRA Document Number 2971197) to determine residues was higher than the Canadian rate. The field trial application rate was 52 oz/acre, which converts to 1.68 kg a.e./ha. The JMPR Report reported the rate as 1.71 acid equivalents/ha. This is almost twice the preharvest application rate of 0.9 kg a.e./ha of Canada. Thus the MRL findings in the bean trials are based on preharvest application rates that are not consistent with, and markedly higher than, those of Canada.

The separation between the application rate for beans for preharvest and other uses is not made in the Summary Report or the Monsanto DEA; all that is reported is a range for the total application rate. Such reporting is not transparent, and also not relevant to residue levels, at least according to the JMPR - all that is relevant is the preharvest application rates. The JMPR Report states (at p. 80) that "[t]he Meeting considered that pre-emergence applications would not contributed significantly to residue levels at harvest", so it did not report on them.

A further concern arises because the preharvest interval (**PHI**) in Canada is 7-14 days, but the Monsanto DEA and the JMPR Report both based the recommend MRL for dry beans on a 7 day PHI. So again, the MRL recommendations are based on an application assumption, ie. that the PHI is just 7 days, that is not applicable in the Canadian context. This is particularly concerning, because, as indicated, the majority of the actual findings in the decline studies for dry bean actually showed an increase, rather than a decline, in residues at day 13 and day 20. This means that the actual Field Trial results showed high residue levels at the point in time that is one day short (day 13) of the longest preharvest interval allowed in Canada (14). Below is a representation of the "decline" study for beans.



Lentils, dry.

With respect to dry lentils, the Monsanto DEA (p.15) indicates results from US dry pea and Canadian and US dry lentil trials field trials were used to determine the recommended MRL 0f 10 ppm on dry lentils, dry field peas and dry pigeon peas**.**

The Monsanto DEA sets out application rates in both Canada and the US, and indicates that in Canada glyphosate is registered on dry peas and dry lentils for preplant, in-crop spot treatment and preharvest use at the same rates as for beans, namely 0.9 to 4.32 kg a.e./ha…. with a similar preharvest interval of 7-14 days. With respect to preharvest use, the 0.9 kg a.e./ha rate and a preharvest interval of 7-14 days is consistent with the rates set out above in PRVD2015-01.

The Monsanto DEA indicates that in the US glyphosate is registered for pre-plant and preharvest applications at the rate of 4.2 kg a.e./ha for pre-plant and 2.5 kg a.e./ha for preharvest, with a preharvest interval of just 7 days.

To the extent the Proposed MRLS will apply to domestic crops, the same initial concern arises with the lentil trials as with the bean trials, namely that the preharvest application rate used in the field trials was a higher application rate than allowed in Canada. The preharvest application rate used in the lentil field trials (PMRA Document Number 2971199) to determine residues were 2.5 kg a.e./ha. This is almost three times the preharvest application rate of 0.9 kg a.e./ha for Canada. Thus the MRL findings in the lentil trials are based on preharvest application rates that are not consistent with, and markedly higher than, those of Canada.

Similar to the reporting on beans, the separation between the application rate for lentils for preharvest and other uses is not made in the Summary Report or the Monsanto DEA; all that is reported is a range for the total application rate. Such reporting is not transparent.

A further concern arises because the PHI interval in Canada is 7-14 days, but the Monsanto DEA and the JMPR Report both based the recommend MRL for dry lentils on a 7 day PHI. So again, the MRL recommendations are based on an application assumption, ie. that the PHI is just 7 days, that is not applicable in the Canadian context.

Although the declines studies for beans showed this was of particular concern because of an increase in residues over the period of the study, the issue of whether there is a concern with lentils is not known. The reason is that, as indicated above, the reporting on the decline study has apparently been removed from the Field Trial study. The reasons for the removal are not known, but removal of results that are not as expected or desired cannot be scientifically justified.

Dry Peas.

With respect to dry peas, the Monsanto DEA (p.15) indicates results from US dry pea and Canadian and US dry lentil trials field trials were used to determine the recommended MRL 0f 10 ppm on dry lentils, dry field peas and dry pigeon peas.

The Monsanto DEA sets out application rates in both Canada and the US, and indicates that in Canada glyphosate is registered on dry peas and dry lentils for preplant, in-crop spot treatment and preharvest use at the same rates as for beans, namely 0.9 to 4.32 kg a.e./ha…. with a similar preharvest interval of 7-14 days. With respect to preharvest use, the 0.9 kg a.e./ha rate and a preharvest interval of 7-14 days is consistent with the rates set out above in PRVD2015-01.

The Monsanto DEA indicates that in the US glyphosate is registered for pre-plant and preharvest applications at the rate of 4.2 kg a.e./ha for pre-plant and 2.5 kg a.e./ha for preharvest, with a preharvest interval of just 7 days.

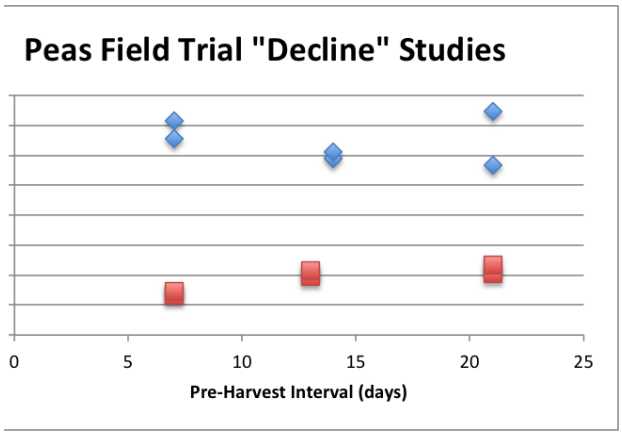
To the extent the Proposed MRLS will apply to domestic crops, the same initial concern arises with the peal trials as with the bean and lentil trials, namely that the preharvest application rate used in the Field Trials was a higher application rate than allowed in Canada. The preharvest application rate used in the peas field trials (PMRA Document Number 2971191) to determine residues were 2.5 lb acid equivalent /Acre, which equates to 2.5 kg a.e./ha. This is almost three times the preharvest application rate of 0.9 kg a.e./ha for Canada. Thus the MRL findings in the peas trials are based on preharvest application rates that are not consistent with, and markedly higher than, those of Canada.

Similar to the reporting on beans and lentils, the separation between the application rate for lentils for preharvest and other uses is not made in the Summary Report or the Monsanto DEA; all that is reported is a range for the total application rate. Such reporting is not transparent, and apparently, according to the study authors, not relevant – all that is relevant is the preharvest application rates. They indicate the results for one location without preplant application was still valid, because “no residues would be expected from the preplant soil application because glyphosate is tightly absorbed to soil”.

A further concern arises because the preharvest interval) in Canada is 7-14 days, but the Monsanto DEA and the JMPR Report both based the recommend MRL for dry peas on a 7 day PHI. So again, the MRL recommendations are based on an application assumption, ie. that the PHI is just 7 days, that is not applicable in the Canadian context.

This is particularly concerning, because of the results of one of the two decline studies. The second decline study the majority of the actual findings showed an increase, rather than a decline, in residues at day 14 and day 21 (and the first study showed just a slight increase). The average residues at days 14 and 20 were almost 1.5 and 1.6 times higher, respectively, than the residues those found at day 7. This means that the actual Field Trial results showed high residue levels at the point in time that equates to

the longest preharvest interval allowed in Canada (14 days). Below is a representation of the "decline" study for peas.



Unjustified Grouping of Lentils and Peas

A final concern with the reporting on the Field Trial results and the JMPR Report, as it relates to the Canadian context, is that JMPR combined the findings on dry lentils and dry peas under "Dry peas, subgroup of". The explanation provided in the JMPR Report was:

> "As the US GAP [Good Agricultural Practice] covers the subgroup of dry peas, the Meeting decided to recommend a maximum residue level for the subgroup of dry peas. The data on lentils and peas, dry, were not significantly different according to the Mann-Whitney U test. The Meeting decided to combine the datasets."

The combination of the two datasets if not justified just because the data on them was not significantly different. The Mann-Whitney U test is "used to compare the differences between two independent samples when the sample distributions are not normally distributed and the sample sizes are small (n <30)". The JMPR Meeting may have decided to combine the datasets because it originally had a small dataset of n=11 with lentils. It went back to 1998 data to add the dataset of n=5 from peas and come up with a dataset of n=16.

Problems with Crop Grouping

PMRA indicates in *Residue Chemistry Crop Groups* that "individual crops are allocated to a crop group based on botanical and taxonomic criteria" and practices. The OECD, in the document OECD Guidance Document on Crop Filed Trials, Second Edition, indicates that subgroups are "primarily indicative of form and growth habit", and that "normally at least one commodity would be needed from each subgroup to set a group MRL". The crop grouping put forward in Table A-1 of the Evaluation Report and Table 2 in the Summary Report is problematic, because the botanical criteria and growth habits of some of the 21 beans listed in the group for the commodity of dry beans are different than those of the others.

Specifically, some of the crops have an indeterminate growth habit, whereas others have a determinate growth habit. As described above, and explained in Wikipedia: "[i]n biology and botany, **indeterminate growth** is growth that is not terminated in contrast to **determinate growth** that stops once a genetically pre-determined structure has completely formed. Thus, a plant that grows and produces flowers and fruit until killed by frost or some other external factor is called indeterminate."

The implication of this is that if the Field Trials on dry beans used for supporting the MRLs were trials on determinate beans, they are not representative of the levels of glyphosate in indeterminate bean plants, and vice-versa.

Preliminary investigation on the 21 crops listed in Table A-1 of the Evaluation Report as being represented by "Dry bean seed" indicates that the list includes some beans with indeterminate growth habits and some with determinate. Dry beans can have either a determinate or indeterminate growth habit. Saskatchewan Pulse Growers states:

> "Two basic plant growth habits are found in dry edible beans, determinate (bush) or indeterminate (vining or trailing). With determinate growth, stem elongation stops when the terminal flowers on the main stem develop. Indeterminate growth means that flowering and pod filling will continue simultaneously or alternately, as long as temperature and moisture availability permits growth to occur."

Alberta Pulse Growers states that "Dry beans have both determinate growth habit (stem elongation will stop when the terminal flowers develop on the main stem), and indeterminate growth habit (will continue to grow and flower until some stress factor induces maturity)."

The Alberta publication "Variety of Pulse Crops for Alberta" describes pink beans and pinto beans as indeterminate, both of which are on the list . The Sask Seed Guide indicates navy beans have both determinate and indeterminate varieties, and Saskatchewan Pulse Growers indicates the same for pinto beans. It is not known whether the Field Trials on dry beans were on a variety with an indeterminate or a determinate growth habit, but regardless of which growth habit they had, the results were not representative or applicable to the varieties with the different type of growth habit.

The Alberta publication also characterized as indeterminate the following beans which are apparently grown in Alberta and/or BC: Great Northern bean and small red bean. It characterized as determinate the yellow dry bean and the cranberry and yellow bean. These beans do not appear to be on the list, so it appears that the default MRL of 0.1 ppm applies to these beans.

Changes to Crop Groups Not Reflected

The Summary Report in Table 1 sets out the food commodities affected by the proposed MRLs, and make reference to crop subgroup 6C. It also states that the MRLs are proposed for each commodity in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage.

However the webpage indicates that original crop grouping 6, including crop group 6C, was revised in 2021 to different crop groupings, under the grouping 6-21, pursuant to *PMRA Guidance Document, Revisions to Specific Residue Chemistry Crop Groups - 2021 update*. Many of the crops in the original crop subgroup are now in crop subgroups 6-21 E and F, but there are others included. Relying on the grouping in the Summary Report yields the result that the other crops that have been included in update crop groups 6-21 E and F should have the default MRL of 0.01 ppm. The commodities that are the subject matter of the Proposal have changed, and the wording in the Proposal is outdated and inaccurate.

Problems with 30% Moisture Content Requirement Used in the DEA

The labels for application of glyphosate require that the product be sprayed at less than 30% seed (grain/ bean) moisture content. As stated in the Monsanto DEA regarding "Residue Information" (p. 15),

"In both countries [US and Canada], the preharvest application must be made when the seed moisture content is less than 30%". The herbicide labels that set out application instructions state this moisture content requirement.

The basis for setting the level of seed moisture content at 30%, rather than a different number, appears to be that that during the stages when a plant is growing and filling seeds with nutrients, the seeds have high moisture content. As the seed is filled and starts to harden, the moisture content declines.

But there is limited if any scientific evidence to support the contention that spraying when the seed moisture content is 30% or less results in pesticide levels in the seed that are not of concern from a risk perspective. No evidence in the public domain or published literature has been found, leading to the proposition that the 30% moisture content is an arbitrary standard.

The concern with the 30% moisture content standard is that compliance with it will not ensure that risks of concern do not arise, for various reasons. Yet the moisture content standard is the standard required in the labels, and the standard on which the Monsanto Dietary Risk Assessment was based on and the standard required of the Field Trials. As such, the consideration of the Monsanto DEA as a measure for risks of concern cannot be supported.

One reason that the 30% moisture content standard is not appropriate is that moisture content is not a determining factor for the level of translocation of glyphosate to the seed. The application of glyphosate in the preharvest field trials is consistently described as being done at a particular stage of "physiological maturity". Moisture content is used in the field trial studies and other studies as one indicia of physiological maturity, as are various visual symptoms (typically regarding pods, not the seeds in the pods). It is submitted that the stage of physiological maturity, rather than moisture content, is a better indicator of the stage of growth in a plant when it is ready to be harvested and growers would want to spray.

A concern arises in that, even if it is accepted that the key indicator for growers on when to spray is the stage when a plant is "physiologically mature" and so ready to be harvested, this does not mean either that a) a physiologically mature plant is no longer accumulating residues in its seeds; or b) that spraying when a plant is physiologically mature does not mean that the resulting level of residue is of low concern from a health risk perspective.

With respect to the first point, it is apparent from the residue "decline" field trial studies described above, that seed residue levels can actually increase, rather than decline, after application date. This is perhaps because of the reasons provided ie. that the plant translocates glyphosate to the growing seeds from whatever the contact location on the plant, provided the plant is growing seeds.

With respect to the second point, no studies have been done to show that the levels of glyphosate residue in the seeds of physiologically mature plants do not pose health risks of concern to humans, even if such limits are below the maximum residue limits. Such studies are required in a valid assessment of the health risks of glyphosate.

All that PMRA does to assess the potential health risks associated with the Proposal is to conduct the DEA by running the DEEM model using the MRLs set in the Proposal, and come to the conclusion that the "proposed MRLs will not pose an unacceptable risk to any segment of the population". But as will be

shown, the DEEM model is out of date and not representative of Canadians. The DEEM model also uses toxicological endpoints at inputs that are much too high, as will also be shown.

A specific analysis of the risks associated with glyphosate residues founds in the seeds of crops when sprayed at the stage of physiological maturity is required. This analysis must be conducted on a crop by crop basis, not on the basis of "crop grouping", as discussed above, because the growth habit of each type of crop is different.

Food and Drugs Act Supports Crop by Crop Assessment

There is a legal basis to support the requirement that a health risk assessment be conducted on a crop by crop basis, rather than on one representative crop for a crop group. The basis is that each crop can be considered a separate "food", and the *Food and Drugs Act* (**FDA**) contemplates an MRL being established and specified under the PCPA for each specific food, as will be explained.

Maximum Residue Limits for pest control products are contemplated in the FDA. The FDA Section 4(1)(d) of the FDA prohibits the sale of an "article of food" that is "adulterated". Section 4(2) sets out an exemption which indicates that a food should not be considered adulterated if the pest control product in or on the food does not exceed the MRLs set under Sections 9 or 10 of the PCPA:

> Exemption
>
> 4(2) A food does not have a poisonous or harmful substance in or on it for the purposes of paragraph (1)(a) — or is not adulterated for the purposes of paragraph (1)(d) — by reason only that it has in or on it a pest control product as defined in subsection 2(1) of the Pest Control Products Act, or any of its components or derivatives, if the amount of the pest control product or the components or derivatives in or on the food being sold does not exceed the maximum residue limit specified under section 9 or 10 of that Act.

The meaning of "adulterated" when it comes to pest control products is set out in Regulation B.15.002(1) of the Food and Drugs Regulations. It contemplate an MRL being set "for that food" under section 9 or 10 of the PCPA:

> B.15.002 (1) Subject to subsection (2), a food is adulterated if
>
> (a) a pest control product as defined in subsection 2(1) of the Pest Control Products Act or its components or derivatives, for which no maximum residue limit has been specified under sections 9 or 10 of that Act for that food, are present in or on the food, singly or in any combination, in an amount exceeding 0.1 part per million (emphasis added).

Sections 9 and 10 of the PCPA, as mentioned, require that a health risk assessment be conducted when MRLs are established under the PCPA.

Comments on the DEA in the Health Risk Assessment

The PCPA requires the Minister (the PMRA) to evaluate the health risks of the pest control product when setting maximum residue limits (sec. 10) and to find such risks acceptable (sec. 11). As stated in the Summary Report, "The PMRA must determine… that such residues will not be a concern to human health".

If it is the case that the PMRA does have jurisdiction to increase MRLs and section 11 of the PCPA applies, then PMRA is obligated to consider various items. For purposes of making these comments on the health risk assessment conducted by PMRA, it is assumed that Section 11 applies.

Under section 11(2), the Minister (PMRA) is to conduct a health risk assessment that takes into account and "consider available information on" various factors (the **Factors**), including, under section 11(2)(a): dietary exposure, exposure from other exposure from other non-occupational sources, including drinking water and use in and around homes and schools; cumulative effects; and the different sensitivities to pest control products. Under section 11(2)(b) it has to apply a 10-fold safety factor for infants and children.

With respect to the Factor of dietary exposure, the Evaluation Report purported to update the dietary exposure assessment, but otherwise did not consider the remaining Factors.

Did Not Consider Available Canadian Consumption Data

The health assessment section of the Evaluation Report states that the dietary exposure assessment for glyphosate was updated and no health risks of concern for acute and chronic dietary exposure (food and drinking water) were identified for any segment of the population, including infants, children, adults, seniors and females 13 to 49 years old.

The Monsanto DEA used for the for the Proposal was called "Dietary Exposure Assessment (DEA) Using DEEM-FCID (NHANES)". It used a dietary consumption evaluation model known as Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c).

The food consumption data used by this model was taken from a 2005-2010 dietary survey of Americans, not Canadians, called the National Health and Nutritional Examination Survey, What We Eat in America (**NHANES/ WWEIA**). Because the data is based on the consumption of Americans, it is not relevant to Canada or what Canadians consume in their diet.

On the above stated assumption that section 11 of the PCPA applies to the Proposal, PMRA Is obligated to consider "available information" on dietary exposure, among other Factors. Dietary consumption data that shows what Canadians eat in Canada was available to the Minister, but PMRA did not consider it. Moreover, it was more up to date than the American consumption data used.

PMRA's August 2018 document "The Use of Dietary Intake Data in Dietary Exposure Assessments within Health Canada" shows that most of the branches of Health Canada obtain their dietary intake data from two Canadian sources: the Community Health Survey – Cycle 2.2. (**CCHS**) and the Nutrition Canada Survey (p.6). The CCHS is a large scale food consumption survey (p.4), that provides food and nutrient intakes on Canadians from birth to over 65 years old. PMRA acknowledges in the document that "[t]he

main limitation identified was that since it is an American study and that there are small sample sizes for specific sub-populations, it may not be representative of Canadian intakes".[2]

CCHS has data on the consumption of foods by Canadians in 2015, in its Food Consumption Table (2015 CCHS-Nutrition). This data is more relevant because it represents data on what Canadians eat, not Americans, and the 2015 data is more up to date than the data of NHANES/WWEIA, which was from 2005-2010.

CCHS also provides data on the appropriate crops. The data set in CCHS on "Meat Alternatives" includes data on Food Group 37 A, which subgroup is called legume. The "Description of the Contents of the Food Sub-groups" is "Includes dry beans- dry peas- lentils- raw- boiled and canned- hummus". Thus there is Canadian dietary consumption data from 2015 on the relevant foods.

Plus the data in CCHS is presented in such a way that it can be put into substantially the same population subgroups as those used in the DEEM-FCID model. The categories of age and sex in CCHS are: Both sexes: all ages; 1-3 year; 4-8 years; 9-13 years; 14-18 years; 19-30 years; 31-50 years; 51-70 years; 71+ years; 1-18 years; 19+years. The categories for each of Males and Females are the same, except they do not include the first two categories (1-3 years; 4-8 years) or 1-18 years.

The categories in DEEM for "All population subgroups, excluding females 13-49 years old") are: All Infants; Children 1-2; Children 3-5; Children 6-12; Males 13-19 years; Males 20-49; Males 50-99. There is a separate category for just Female 13-49.

PMRA provides the justifications for using the US data in SPN2014-01 *General Exposure Factor Inputs for Residential, Occupational and Dietary Exposure*. In that document, it provided reasons for its adoption of the DEEM model even while noting there are differences between Canadian and US consumption patterns in that Canadians eat more fresh vegetables and fruits and less processed food than Americans:

> "Comparison of NHANES and Canadian Dietary Consumption Data
>
> Canadian dietary consumption data from the CCHS cycle 2.2 (2004) were available in addition to the [American] consumption data from WWEIA. The PMRA conducted a preliminary analysis of food consumption patterns in Canada versus the US. The major food commodities in American and Canadian markets were generally similar and were available to most of the population. However, the preliminary analysis of the CCHS cycle 2.2 (2004) and NHANES-WWEIA (2003-2006) surveys indicated that the intake of processed commodities is higher in the United States while the consumption of fresh vegetables and fruits is generally higher in Canada. Overall, there were differences identified for 16% of the total number of raw agricultural commodities in the food supply; however, the nature and quality of the datasets precluded further characterization of these differences."

The reasons provided by PMRA for its adoption of the US consumption data and the DEEM model are not supportable. It indicated the US data had a larger sample size, but as indicated above, CCHS is a large scale consumption survey. It indicated NHANES/WWEIA is a continuous survey, but so is CCHS. It indicated the US consumption data allowed for probabilistic assessments to be conducted, but such an

[2] PMRA in the document used the "Continuous Survey of Food Intake by Individuals", a successor to the original US dietary consumption data used by PMRA in the DEA, but both used only consumption data of Americans.

assessment could likely be similarly conducted with the CCHS data. Moreover, as will be shown, the PMRA does not conduct probabilistic assessments. PMRA indicated NHANES/WWEIA has comprehensive data for identifiable subgroups, but, as shown above, so does CCHS.

It is clear that at the time PMRA conducted the updated DEA, it had information "available" that was more up to date and relevant than the US data used. The available data was on what Canadians eat (not Americans), it was from 2015 (not 2010), and it provided information on relevant populations subgroups and food types. PMRA was not acting in accordance with the letter of the law (section 11), or the purpose of the PCPA by using the outdated American data.

Methodology Concerns with Respect to Percentiles and Deterministic Assessments

PMRA sets out its policy on what percentile to use as a threshold of concern in acute dietary exposure assessments, in its Science Policy Note SPN 2003-01 *Choosing a Percentile of Acute Dietary Exposure as a Threshold of Concern* (**SPN2003-01**). It states (in the Executive Summary):

> "PMRA intends to use the 99.9th percentile of distribution of estimated acute dietary exposure exposures for calculating the TOC [Threshold of Concern] when probabilistic exposure assessment techniques are used to model the distribution".

PMRA also indicates that as of 2003 it is using the probabilistic techniques and the associated 99.9th percentile approach for acute exposure assessments (as opposed to chronic):

> "The PMRA is using Monte Carlo techniques (and its current 99.9th percentile approach) for these acute food exposure assessments only". (at p.3)

The reason the probabilistic method is preferred is it provides a more realistic estimate of exposure. Rather than just inputting one MRL value into the dietary exposure assessment, it uses the entire range of residue data from the numerous crop field trial studies (or other sources) together with the range of consumption values (SPN2003-03, p. 24).

However, in the September 3, 2020 Monsanto DEA relied upon by PMRA, results on the acute assessment of food only were reported using a <u>deterministic</u> analysis at the 95th percentile, stating:

> "The basic acute dietary exposure for all supported glyphosate registered and imported commodities was estimated to be 29.1% of the ARfD for females 13-49 years of ages and 12.3% to 44.8% of the ARfD for all other population subgroups (95th percentile, <u>deterministic</u>)". (p.4 Monsanto DEA, emphasis added)

PMRA recommends that risk assessors in a deterministic analysis use the 95th percentile, so that "PMRA does not unreasonably overprotect [significant subpopulations]". (SPN2003-01, p.21). But by not reporting at the 95th percentile, the PMRA is not protecting the 5% of the population that in theory is above the 95th percentile. The standard of "reasonable certainty of no harm" is not met with such an analysis, because it cannot be said with reasonable certainty there is no risk of harm to that 5%.

When presented at the 95th percentile, the data do not show exceedances of any thresholds. Such is not the case with the reporting at the higher percentiles. The data on this deterministic assessment at the

99th and 99.9th percentile for children 1-2 years old from the Monsanto DEA are set out below. The data shows exceedances of the 100% threshold of concern in both instances: at the 99th percentile, the % aRfd was 128.64, and at the 99.9th percentile, the % aRfd was 321.34. An exceedance equates to a risk of concern. PMRA did not address these exceedances.

Summary calculations – per capita:

	--- 95th percentile ---			--- 99th percentile ---			--- 99.9th percentile ---		
	Exposure	%aRfD	MOE	Exposure	%aRfD	MOE	Exposure	%aRfD	MOE
Children 1-2	0.447972	44.80	223	1.286360	128.64	77	3.213391	321.34	31

In the September 3, 2020 Monsanto DEA relied upon by PMRA, the results on the "basic acute aggregate assessment of food & drinking water were also based on results at the 95th percentile and also showed risks of concern at higher percentile levels. The results were reported as follows:

> "Aggregate exposure from food and drinking water (EEC value = 267 µg a.i./L, Level 2, surface water, reservoir) is not of health concern. Specifically 30.3% of the ARfD was obtained for females 13-49 years of age and 12.9% to 46.2% of the ARfD for all other population subgroups". (p.4 Monsanto DEA)

However, the results were different at higher percentile levels. The data on this basic acute deterministic assessment at the 99th and 99.9th percentile for infants and children 1-2 years is presented below, and shows exceedances of the 100% threshold of concern in three instances: at the 99th percentile, the % aRfd was 129.03 for children 1-2, and at the 99.9th percentile, the % aRfd was 116.78 for infants and 322.06 for children 1-2. This means there were three risks of concern identified at percentile levels higher than the 95th. The PMRA did not report or comment on these results.

Summary calculations – per capita:

	--- 95th percentile ---			--- 99th percentile ---			--- 99.9th percentile ---		
	Exposure	%aRfD	MOE	Exposure	%aRfD	MOE	Exposure	%aRfD	MOE
Infants	0.357193	35.72	279	0.498413	49.84	200	1.167777	116.78	85
Children 1-2	0.461559	46.16	216	1.290310	129.03	77	3.220556	322.06	31

The policy of the PMRA is to conduct probabilistic, not deterministic, assessments when conducting aggregate exposure assessments. In policy document SPN2003-01 PMRA requires that aggregate risk assessments be conducted at the 99.9th percentile and that this percentile is needed to assure safety. It states in the Executive Summary that the safety standard for maximum residue limits is called the Threshold of Concern (TOC), and it is the threshold at which dietary exposure from aggregate food residues is considered safe. It indicates:

> "[T]he TOC is the point at which the aggregate exposure from food residues, at 99.9%, is equal to the acute reference dose. This concept is the basis of this policy/ guidance document".

The US Environmental Protection Agency also requires analysis at the 99.9th percentile. As reported by Charles Benbrook[3], "The EPA has interpreted the FQPA's [Food Quality Protection Act] "reasonable certainty of no harm" to mean that the daily exposure level for a given pesticide at the 99.9th percentile of its exposure distribution should be below the pesticide's cRfD [chronic reference dose] or cPAD [chronic population adjusted dose after factor adjustment]".

There is no scientific justification for PMRA to not conduct a probabilistic, rather than a deterministic, analysis in its aggregate risk assessments. In the Monsanto DEA, the aggregate assessment is explained as a "basic acute" assessment, but this concept is not explained. It appears, however, from an explanation on p. 4 of the Monsanto DEA that this "basic acute" analysis was conducted using "Canadian MRLs, American tolerances for imported commodities, default processing factors, as well as the assumption that 100% of the crops are treated", which align with the deterministic method.

In its policy SPN2003-03, PMRA explains that probabilistic assessments are required in order to attain information on more realistic residues for aggregate and cumulative assessments, which are needed to make informed regulatory decisions that protect the public. It states:

> "PMRA anticipates that refinements will be key to developing more realistic estimates of the actual residue levels on food as the PMRA proceeds through the aggregate, and particularly the cumulative, assessment of pesticides. More realistic residue estimates ultimately improve the Agency's ability to make informed regulatory decisions that fully protect public health and sensitive subpopulations, including infants and children."

It states (at p.21) that "[w]ith the aggregate and cumulative assessments now required, it is likely that higher tier (Tiers 3 and 4) exposure estimates will be needed". The "higher tier" assessments use probabilistic analysis.

Given that the aggregate risk assessment to be protective requires a probabilistic assessment be conducted, it behooves the PMRA to obtain the data to conduct such assessments. The PCPA requires an aggregate risk assessment be conducted in the health risk assessment (section 9) and PMRA by its own policy indicates probabilistic assessments and realistic residue limits are needed for aggregate and cumulative assessments.

In SPN2003-03 PMRA indicated that at that time, "the probabilistic technique can be used only for acute assessment because of limitations in the consumption database". But if PMRA cannot obtain the data, it does not have the data required to conduct a valid risk aggregate or cumulative assessment and is not in compliance with the "scientifically based approach" of the PCPA.

The need for more refined approaches has been recognized the literature, given the large increases of glyphosate use in North America since the mid 2000s, particularly with respect to preharvest use. The author of a piece on trends of glyphosate use worldwide speaks to the issue of not having adequate data and suggests an approach that could be used:

[3] Benbrook, C. and Davis, D. The dietary risk index system: a tool to track pesticide dietary risks. Environmental Health (2020) 19:103, 17 https://doi.org/10.1186/s12940-020-00657-z

> "The frequency and levels of glyphosate and residues in a variety of foods are increasing, and more refined dietary-risk assessments should be carried out. Reasonably accurate estimates of glyphosate residues and dietary exposures in areas lacking residue data can be made drawing on insights gained from risk assessments conducted in areas with accurate glyphosate use and residue data."[4]

Health Risk Assessment Did Not Conduct a Cancer Risk Assessment

The Monsanto DEA "was based on the DEA which was conducted to support the re-evaluation of glyphosate published in PRVD2015-01 and the RVD2017-01" and referenced monographs (Monsanto DEA p.2). The Monsanto DEA also set out certain changes to the DEA used for PRVD2015-01 and RVD2017-01 as a result of the submission S2019-1027 for the establishment of MRLS for residues of glyphosate and the metabolite AMPA (expressed as glyphosate) in/on imported dry peas and dry beans from crop subgroup (SCG) 6C and tree nuts from crop groups (CG) 14-11. The " notable changes included in conducting this updated DEA" included the updated proposed Canadian MRLs on beans and pea.

The DEA conducted to support the Preliminary Re-evaluation decision (PRVD2015-01) and final Re-evaluation Decision (RVD2017-01) of PMRA on glyphosate was an *August 2, 2013 Monograph Food Residue and Dietary Risk Assessment* of PMRA (**2013 Dietary Monograph**). In Section 3 "Hazard Characterization/Toxicological Endpoints Selection" it discussed three hazard characterizations: acute, chronic and carcinogenic dietary hazard characterizations.

The acute (1 day) dietary hazard characterization provided an endpoint of an Acute Refence Dose ((**ARfD**) of 0.5 mg/kg bw for females aged 13-49 years old, and an ADI of 1.0 mg/kg bw for all other subpopulations.

The chronic (long-term) dietary hazard characterization provided an endpoint of an Acceptable Daily Intake (**ADI**) of 0.32 mg/kg bw/day.

The carcinogenic dietary hazard characterization did not provide an endpoint. The reason provided in the 2013 Dietary Monograph (p.11) was "No cancer risk concerns were identified [Toxicology Re-Evaluation, PMRA #2222272]".

PMRA did not conduct a risk assessment for cancer or turn its mind to the hazards associated with glyphosate associated with cancer in conducting its health risk assessment for the Proposal. It presumably relied upon the findings of 2015-01 in this regard. However, the scientific literature since PRVD2015-01, has provided strong evidence of the carcinogenic risks of glyphosate that warrant assessment. This literature at a minimum raises a scientifically founded doubt about the stance that a cancer risk assessment need not be conducted.

In the face of the International Agency for Research on Cancer (**IARC**) 2016 classification of glyphosate as a Group 2A carcinogen—that glyphosate *probably* causes cancer in humans—it is surprising to see a single-paragraph discussion of cancer in the Toxicology Monograph, large data gaps, and no risk assessment. The Monograph paragraph includes the statement:

[4] Benbrook, C. Trends in glyphosate herbicide use in the United States and globally Environ Sci Eur (2016) 28:3, 14. DOI 10.1186/s12302-016-0070-0

> "In consideration of the strength and limitations of the large body of information on glyphosate, which included multiple short and long term (lifetime) animal toxicity studies, numerous in vivo and in vitro genotoxicity assays, as well as the large boy of epidemiological information the overall weight of evidence indicates that **glyphosate is not unlikely to pose a human cancer risk**."

This was altered to, "… glyphosate is unlikely to pose …" in PRVD2015-01. In neither the Monograph nor PRVD15-01 was a formal systematic review or weight of evidence analysis presented, and cancer was not included as a toxicological endpoint.

Indeed, the Toxicology Re-Evaluation Monograph (**2015 Toxicology Monograph**) did identify cancer risk concerns relating to oncogenicity and cytotoxicity, as well as immunotoxicity. For example, with respect to oncogenicity, PMRA reported that studies PMRA #11661786 and #1161795, the 1993, Glyphosate 104 week dietary carcinogenicity study in mice, DACO: 4.4.1, 4.4.2 found "…equivocal evidence of oncogenicity." This evidence was dismissed with the following "Comment" (p. 89): "It was noted that a slight increase in the number of animals in the high dose group of both sexes having multiple tumour types, which led to an overall increase in the total number of tumours in these groups. Due to the lack of histological evidence an increase in any tumour type [sic], and because the high dose was the limit dose of testing and would be irrelevant to chronic human exposure scenario, this finding was not considered a sign of carcinogenic potential of glyphosate." This seems to say that the study lacked the standard tumour histology reports, in which case it would have been critically deficient.

Of note, high doses are used in animal carcinogenicity studies to detect effects in limited numbers of animals; otherwise studies would be under-powered.

PMRA could not help but be aware that carcinogenicity of glyphosate has received considerable attention since 2015—scientifically and in the public eye—that would justify an updated review of the scientific literature and animal toxicology, as well as cancer risk assessment to inform dietary intake and risks before increasing MRLs.

Animal toxicology studies with an oral route of exposure are directly applicable to dietary assessments. The PMRA did not, in fact, consider all available long-term chronic carcinogenicity studies available to regulators at the time of the glyphosate MRL Proposal. Six chronic toxicity/oncogenicity studies presented in the Toxicology Monograph have the data largely redacted, but these industry-sponsored studies are used in many jurisdictions, and the PMRA should have examined the body of evidence that was available internationally. Glyphosate studies available in the European Union were reviewed by Portier (2020), "A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies."[1] Dr. Christopher Portier is a renown scientist and past Director of the U.S. Agency for Toxic Substance and Disease Registry, with decades of scholarly works and leadership in toxicology, methodology, and design, analysis and interpretation of environmental health data, including cancer biology. The abstract summarizes available regulatory animal toxicology studies (emphasis added):

> …twenty-one chronic exposure animal carcinogenicity studies of glyphosate are identified from regulatory documents and reviews; **13 studies are of sufficient quality and detail to be reanalyzed in this review** using trend tests, historical control tests and pooled analyses. Considering analyses of the individual studies, the consistency of the data across studies, the

> pooled analyses, the historical control data, non-neoplastic lesions, mechanistic evidence and the associated scientific literature, the tumor increases seen in this review are categorized as to the strength of the evidence that glyphosate causes these cancers. **The strongest evidence shows that glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice, hemangiomas and malignant lymphomas in female CD-1 mice, hemangiomas in female Swiss albino mice, kidney adenomas, liver adenomas, skin keratoacanthomas and skin basal cell tumors in male Sprague-Dawley rats, adrenal cortical carcinomas in female Sprague- Dawley rats and hepatocellular adenomas and skin keratocanthomas in male Wistar rats.**

In conducting risk assessments, Health Canada requires PRMA to "get the science right, and get the right science" (*Health Canada's Decision-Making Framework for Identifying, Assessing and Managing Health Risks*). Despite the fact that the above studies should have been accessible to and accessed by PMRA, PMRA's 2015 Toxicological Monograph, 2013 Dietary Monograph and PRVD2015-01 included less than half of the available studies, and PMRA did not define an endpoint for cancer risk. Further, In spite of the existence of the large U.S. authoritative review of glyphosate by the U.S. Agency for Toxic Substances and Disease Registry[2] (available in draft in 2019),[3] there was no update when considering increasing MRLs.

The selection of an endpoint by PMRA was required for a risk assessment for cancer. PMRA, in Science Policy Note SPN2003-03, "Assessing Exposure from Pesticides, A User's Guide", July 28, 2003 (**SPN2003-03**), explains that risk requires an examination of both hazard and exposure: (p.3):

> **Exposure and risk at a glance**
> To determine whether any risk can result from either short-term (i.e., acute) or longer term (i.e., chronic) exposure, one considers both the toxicity of the pesticide (which is sometimes referred to as hazard) and the amount of pesticide to which an individual may be exposed.
>
> In the actual risk equations, which are discussed below, toxicity is expressed as: an acute reference dose (ARfD) an acceptable daily intake (ADI) and a potency factor for cancer called the q*. Which toxicity expression the risk assessor uses depends on the duration of exposure (e.g., acute or chronic) and, in the case of a carcinogen, the method chosen for quantifying risk….
>
> The amount of pesticide to which an individual is exposed (i.e., exposure) is determined by combining the amount of pesticide that is in or on the food (i.e., residue levels) and the amount and type of foods that people eat (i.e., food consumption).

When describing the "Toxicological Points of Departure for Use in Human Health Risk Assessment" Table III.2 (p. 91 PRVD2015-01), PMRA does not set out toxicological endpoints required for conducting a hazard assessment, but instead just states "Low level of concern due to benign nature of tumours observed at the limit dose and lack of oncogenicity in other studies." This statement is not justified given the human epidemiology as described below, or given observations of effects reasonably expected to culminate cancer (e.g., inflammatory and immune effects; endocrine related effects) described below.

PMRA takes the position that a cancer toxicological endpoint is not necessary even though PMRA in the 2013 Dietary Monograph discussed the selection of endpoints and assessments for cancer risks, being classified as non-threshold (linear) or threshold (nonlinear) as follows in SPN2003-03:

> **Linear**
> The strength of a non-threshold carcinogen exhibiting a linear dose-response curve is characterized by a potency factor called q1 *, which can be thought of as the slope of the dose-response curve. Non-threshold cancer risk is expressed as a probability calculated from the product of exposure and q1 *.

The failure to select an endpoint for cancer has not been justified, including with respect to carcinogenic effects that are thought to occur through a linear response. The toxicity portion of the risk equation is described in SPN2003-03 (p. 6) as the cancer potency factor that "can be thought of as the slope of the dose-response curve," that in reality is a single number that is calculated from animal data using a sophisticated computer model that assumes linearity at low doses. "The higher the q1* value, the more potent the chemical is as a carcinogen".

With respect to carcinogenic effects that are thought to occur through a non-linear response, PMRA states in SPN2003-03 (p. 6):

> **Nonlinear**
> For carcinogenic effects that are shown to exhibit a nonlinear response, the toxicity portion of the risk equation is expressed as Point of Departure or PoD. A PoD is simply the toxic dose that serves as the "starting point" in extrapolating a risk to the human population. The PoD can be either an observed dose (e.g., NOAEL) or it can be an interpolated value. Quite often, the PoD is equivalent to the NOAEL.

In 2003, PMRA was not prepared to assess nonlinear cancer risks, for the reason that it had not determined an appropriate nonlinear cancer exposure target (p.10): "Nonlinear cancer risk is calculated using the MOE approach where a margin of exposure (MOE) would be calculated. For nonlinear cancer risk assessment, the PMRA has not yet determined an appropriate target MOE. It is currently developing criteria by which to make that judgment."

PMRA did not conduct a cancer assessment even though at the time it was aware of the IARC findings of cancer hazards, and that this was established in part on the basis of epidemiological studies—that is, studies that incorporate by the nature of the research, the exposure resulting from use of glyphosate according to label directions. PMRA reiterated low concern for cancer as a result of glyphosate exposure, and stated in PRVD2015-01 (p. 15):

> The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) recently assigned a hazard classification for glyphosate as "probably carcinogenic to humans". It is important to note that a hazard classification is not a health risk assessment. The level of human exposure, which determines the actual risk, was not taken into account by WHO (IARC). Pesticides are registered for use in Canada only if the level of exposure to Canadians does not cause any harmful effects, including cancer.

This explanation indicates PMRA was aware of the hazard assessment of another body, and understood that both the hazard and exposure assessment are necessary for a risk assessment. It is the case that a low hazard with high exposure is still a concern, but PMRA chose to not apply its own risk assessment methodology at all to cancer. The results is the possibility that Canadians may be developing cancers as a result of over-exposure to glyphosate was put aside. This was despite the fact that the DEEM dietary exposure model contemplates an assessment of cancer risks (Sept. 30, 2014 EPA *Dietary Exposure Evaluation Model, User's Guide*). Rather than conduct a cancer risk assessment, PMRA in PRVD2015-01 just made a "weight of evidence" statement (at p.15):

> **Cancer Assessment**
> In consideration of the strength and limitations of the large body of information on glyphosate, which included multiple short and long term (lifetime) animal toxicity studies, numerous in vivo and in vitro genotoxicity assays, as well as the large body of epidemiological information, the overall weight of evidence indicates that glyphosate is unlikely to pose a human cancer risk.

New Evidence of Cancer Justifies a Cancer Risk Assessment

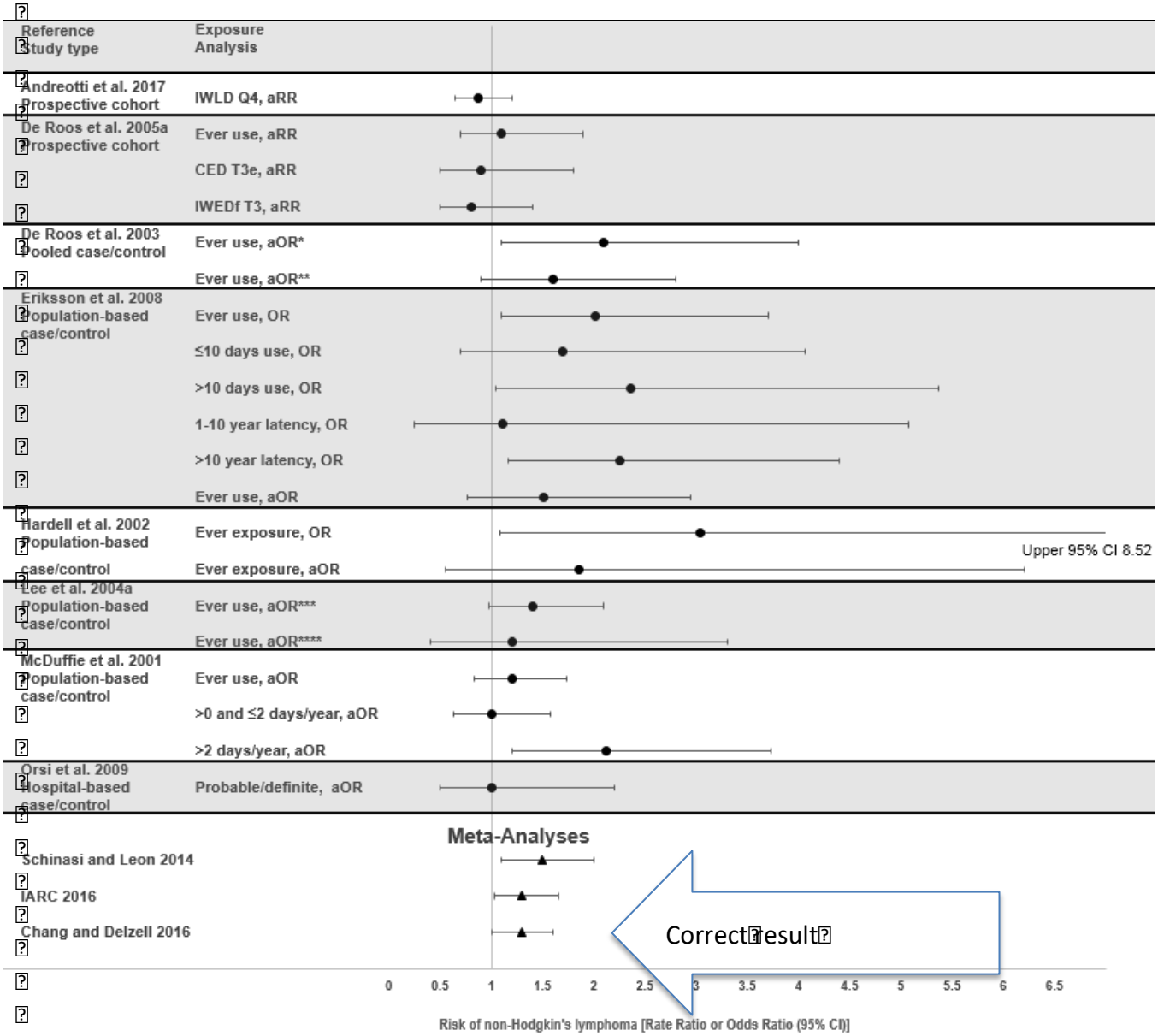
Since the publication of PRVD2015-01, considerable evidence has been published in the scientific literature regarding cancer, and conditions contributing to oncogenesis, with exposure to glyphosate. Some of this body of work supports lines of evidence that do not appear to have been considered by PMRA in PRVD2015-01, and so cannot be considered to have been dismissed via the previous "weight of evidence" statement made in 2015.

In a large effort, the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, in August 2020 published a *Toxicological Profile for Glyphosate* (**ATSDR Report**). This report found positive associations between glyphosate and selected lymphohematopoietic cancers, including non-Hodgkin's lymphoma and multiple myeloma, as summarized at p.6:

> Cancer Effects. The carcinogenic potential of glyphosate has been evaluated in six meta-analyses (Chang and Delzell 2016; IARC 2017; Schinasi and Leon 2014; Leon et al. 2019; Pahwa et al. 2019; Zhang et al. 2019a) and a number of case-control and cohort epidemiology studies (see Section 2.19 for detailed information and specific citations). The meta-analyses reported positive associations between glyphosate use and selected lymphohematopoietic cancers. Most of the case-control and cohort studies used self-reported ever/never glyphosate use as the biomarker of exposure, and subjects were likely exposed to other pesticides as well. Numerous studies reported risk ratios greater than 1 for associations between glyphosate exposure and risk of non-Hodgkin's lymphoma or multiple myeloma; however, the reported associations were statistically significant only in a few studies.

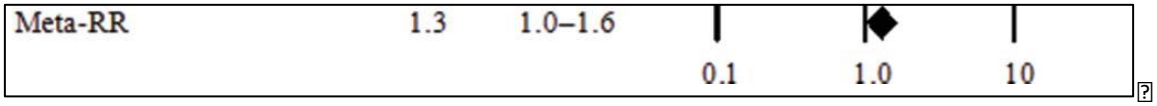
The findings of the ATSDR Report are valid, but a concern arises. Awareness is high regarding "captured agencies" and third parties' inappropriate influence in scientific processes. The ATSDR final report offers a cautionary tale for the PMRA. Along with findings of haematological cancers in epidemiological studies, the report contained an error that was introduced in the Final, but not in the Draft. In spite of intervening publication of positive studies, this error was sufficient to reduce the significance of the final meta-analyses. The following pages are reproduced from the DRAFT and final ATSDR reports.

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

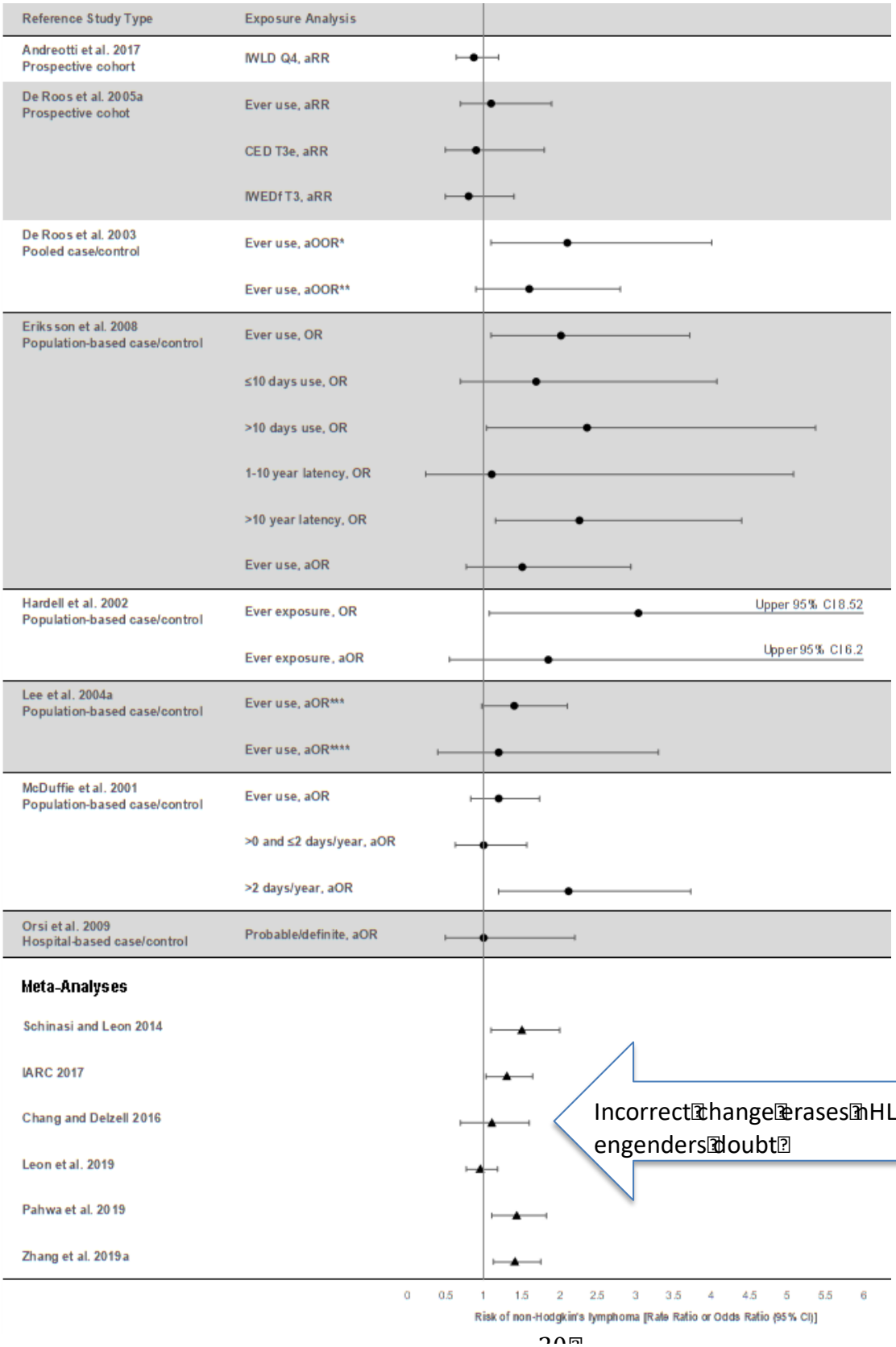


*Logistic Regression; **Hierarchical regression; ***Non-Asthmatic farmers; ****Asthmatic farmers
a = adjusted; CED = cumulative exposure; IWED = intensity-weighted exposure days; IWLD = intensity-weighted lifetime days; OR = odds ratio; Q4 = 4th quartile; RR = rate ratio; T3 = 3rd tertile

Extract from Figure 1. Chang and Delzell[4] "Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers." The odds ratio point estimate is 1.3, with a 95% confidence interval of 1.0 to 1.6.



Toxicological Profile for Glyphosate (ATSDR)
August 2020
Figure 2-4. Risk of non-Hodgkin's Lymphoma Relative to Self-Reported Glyphosate Use or Exposure (notes the same as above)



Incorrect change erases nHL signal, engenders doubt

Epidemiological Studies Show Cancer but are Dismissed

Health Canada in PRVD2015-01 took the position that certain epidemiological studies it reviewed could not be used for regulatory purposes because the exposure was not well characterized. This exclusion of real world evidence of harms is difficult to square with the primary mandate of the PMRA to protect health, and to consider concerns that raise a scientifically founded doubt about the assessments. Epidemiological studies raise such concerns.

Positive epidemiological studies must be presumed to have been conducted in the context of adherence to label directions, and therefore to represent exposures below applicable limits. When human samples for biomarkers (e.g., blood, for levels of pesticides) are collected this information should be able to be compared to representative Canadian results. Inexplicably, glyphosate—Canada's most-used pesticide by far—has never been measured in the Canadian Health Measures Survey. PMRA could identify risks raised by epidemiological studies and explore how to connect animal studies with human data by requiring data and measuring biomarkers to facilitate inter-species extrapolation, in both directions.

Despite uncertainties in measurements in the "real world," epidemiological studies merit considerable weight in pesticide regulation. We see below that results in animal and human studies continue to be reported, that are consistent with the Health Canada study by Arbuckle et al. (2001) "An Exploratory Analysis of the Effect of Pesticide Exposure on the Risk of Spontaneous Abortion in an Ontario Farm Population,"[4] finding late abortions associated with preconception exposure to glyphosate (OR = 1.7; 95% CI, 1.0–2.9).

This represents two decades of missed opportunities to prevent harms to the next generation, and to subsequent generations.

Further Toxicological Evidence Impacting Endpoints

The Proposed Re-evaluation Decision PRVD2015-01 presented evidence of the toxicology of glyphosate, but since the release of PRVD2015-01, additional evidence of the toxic effects of glyphosate has been published in the scientific literature. In addition to cancer, there are serious concerns of, at a minimum, genotoxicity, effects on the microbiome and numerous related outcomes, immunotoxicity, prenatal developmental toxicity and reproductive toxicity, arising with the use of glyphosate and glyphosate-based herbicides. This evidence includes toxic effects at exposure levels seen in the Canadian population, eating foods that we assume comply with current MRLs, and are lower than the regulatory levels proposed by PMRA and used in the dietary risk assessment. Significant epidemiological findings demonstrate that the MRLs are already too high and should be lowered, not increased.

Glyphosate and its metabolite AMPA affect multiple biological pathways, as reviewed by Marino et al., "Pleiotropic Outcomes of Glyphosate Exposure: From Organ Damage to Effects on Inflammation, Cancer, Reproduction and Development."[5] An excerpt:

> Glyphosate has been detected in urine, blood and maternal milk and has been found to induce the generation of reactive oxygen species (ROS) and several cytotoxic and genotoxic effects in vitro and in animal models directly or indirectly through its metabolite, aminomethylphosphonic acid (AMPA). This review aims to summarize the more relevant findings on the biological effects and underlying molecular mechanisms of glyphosate, with a particular focus on glyphosate's

potential to induce inflammation, DNA damage and alterations in gene expression profiles as well as adverse effects on reproduction and development.

Genotoxicity

In the absence of near-consensus among experimental reports, the PMRA and the ATSDR concluded that glyphosate and its herbicide products are not genotoxic to a variety of cell types. Numerous assays of genotoxicty of glyphosate—both the technical ingredient without formulants, and the glyphosate-based herbicide—are included in the PMRA Toxicological Monograph and the ATSDR Toxicological profile. Results of these assays can be sensitive to experimental conditions and the choice of methodologies.

In a nuanced contrast, IARC stated that while glyphosate-based herbicides are not genotoxic to bacteria, **they are genotoxic to mammalian cells**, as well as in studies of genetic damage to community members exposed to herbicide formulations (studies of spraying coca in South America).

Microbiome effects related to neurological impacts, endocrine disruption, inflammatory bowel disease and colorectal cancer

In RVD2017, PMRA provided its response to comments submitted on PRVD 2015. Comments included that glyphosate impacts the human intestinal microbiome and that this can harm humans. PMRA dismissed the reports by essentially saying that this could not be the case (RVD p. 30), and that studies in the lab that show this are not sufficient:

> "Glyphosate targets an amino acid synthesis pathway in plants that is shared by certain types of bacteria, but not humans. 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 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."

Notably, in its response, PMRA overlooked the numerous animal studies that reported frequent soft stools, diarrhea and blood in excrement in the Toxicological Monograph and PRVD2015-01 (Study numbers: 1184851, 1212011, 1411000, 1211035). Similarly, it is reported in the ATSDR Toxicological Profile for glyphosate that at the *lowest* exposure levels there is frequent experimental incidence of soft stools and diarrhea. As confirmed in the recent research reported above, this property has long been considered to be rooted in glyphosate's inhibition of the Shikimate pathway in gut bacteria, that confers its herbicidal as well as antibiotic properties. An acute exposure to glyphosate results in transient disturbance of the microbiome,[6] and reduced synthesis of aromatic amino acids that are essential for health (e.g., neurotransmitters for brain function).

Glyphosate has been reported to disrupt the microbiome of birds,[7] rodents,[8,9,10] and honey bees.[11] On the other hand, removal of glyphosate from the diet may relieve intestinal dysbiosis, because some beneficial bacteria are susceptible, while pathogenic *Clostridia* and *Salmonella* strains are resistant and thrive as other species are removed from the microbiome.[12] Chronic exposures can result in ongoing shifts in the microbiome, with inflammation, oxidative stress and tissue damage along the lining of the gut. Further complexity arises because the formulants in glyphosate-based-herbicides potentiate and/or cause additional cumulative effects on endocrine and reproductive pathways, such as interaction with androgenic and estrogenic pathways.[13]

Since the risk assessment in PRVD 2015-01 and the final registration decision RVD2017-01, published science confirms that, as predicted, glyphosate does indeed affect the human microbiome, that glyphosate exposures harm foetal health, and that effects on health can extend through several generations. In other words, as described in the context of prenatal developmental toxicity below, glyphosate exposure during pregnancy may affect great-grandchildren. The information to date is conclusive, which means the assumption made by PMRA that glyphosate does not affect the microbiome is no longer plausible.

The long-term effect of three doses of Round-up herbicide, a glyphosate product, on the gut microbiome of rats was reported by Lozano *et al.* (2018) "Sex-dependent impact of Roundup on the rat gut microbiome."[14] The herbicide had a direct effect on rat gut microbiota, and various strains of bacteria had different sensitivities to Round-up. Overall the gut microbiome changes were sex-dependent, and overlapped substantially with reported liver dysfunction.

Further evidence of effects of Roundup on the rat gut microbiome, that in turn affected maternal behaviours and brain plasticity, was published by Deschartes *et al.* (2019) "Glyphosate and glyphosate-based herbicide exposure during the peripartum period affects maternal brain plasticity, maternal behaviour and microbiome."[15]

Modern molecular profiling techniques were used to demonstrate that glyphosate or Roundup inhibit the shikimate pathway in the microbiome of rats, by Mesnage *et al.* (2021) "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 Rat*.*"[8] Of relevance to humans, the bacterial species inhibiting the human GI tract are also sensitive to glyphosate-mediated EPSPS inhibition, and substances produced in the context of dysbiosis also cause oxidative stress.

Colorectal Cancer

In recent years, a mounting body of evidence has illuminated roles of the microbiome in digestion, metabolism of food and xenobiotics, and gut health,[16] as well as increased incidence of obesity, inflammatory bowel disease, allergies and cancer outcomes.[17] This is seen clinically in Canada, as inflammatory bowel disease incidence increased 7.2 percent per annum in children aged 5 years and under, from 1999 to 2010,[18] while (related) colorectal cancer incidence increased at 6.4 percent per annum in men aged 20 to 29 years, from 1971 to 2015.[19] Etiological factors in these similar rapid increases in intestinal diseases related to the microbiome, that may certainly be affected by glyphosate based herbicides, merit further research, and precautionary approaches in the interim. With a veritable explosion of research revealing the importance of the microbiome and the metabolome through all life stages and intergenerationally, it is essential that the PMRA recognize effects on the microbiome as a target resulting in adverse effects.

The PCPA requires the PMRA to use a "scientifically based approach" when conducting risk assessments. This requires looking at current and available evidence; re-examining assumptions in the light of further evidence, and providing weight to relevant, important research findings.

Immunotoxicity

The immune system is intimately connected with gut health, and alterations of intestinal microbiome can cause inflammation, as well as activate T-cell immunity.[16]

With respect to immunotoxicity, PMRA [in PRVD 2015-01] reports that study PMRA #2223081 "2012, Glyphosate- a 28 day oral (dietary) immunotoxicity study in female B6C3F1 mice, DACO: 4.8" found "evidence of immunotoxicity"; spleen cells were non dose-responsive. The Comment (p. 114) in the Toxicology Monograph states: "The assessment of immunotoxicity was based primarily on the results of a splenic antibody-forming cells (AFC) assay to assess the T-cell dependent antibody response (TDAR) to sheep red blood cells (sRBD). Other parameters of possible immunotoxicity included the thymus and spleen weights."

PMRA's Science Evaluation in the 2015 Toxicology Monograph on this study agreed with the finding of an altered immune system (p.12):

> In a 28-day immunotoxicity study, dose-related increased T-cell dependent antibody response, as measured by IgM AFC/106 spleen cells, and increased total spleen activity, as measured by IgM AFC/ spleen x 103 , were observed in all treated animals. In addition, a non-dose related increase in spleen cellularity was noted starting in the mid-dose group. Although this test was designed to examine immunosuppression, **an altered function of the immune system could not be ruled out.**

The ATSDR Report (p. 85) pointed to the Kumar et al. (2014)[20] study focusing on occupational asthma and respiratory conditions. They reported an inflammatory respiratory response in anesthetized mice exposed intranasally to glyphosate. This is consistent with Agriculture Health Study and Canadian findings of associations of allergies and asthma exacerbations of pesticides exposures, including glyphosate.

The immune system is increasingly being recognized as mediating toxic effects. A recent example is Liu *et al*. (2022) "Glyphosate-induced gut microbiota dysbiosis facilitates male reproductive toxicity in rats"[21] that revealed that glyphosate-related testicular damage resulted from microbiome dysbiosis, that correlated with decreased sperm quality, mediated by Interleukin-17A signalling.

Prenatal Developmental Toxicity

With respect to Prenatal Developmental Toxicity, Section 1.6 of Toxicological Monograph (p.9) PMRA reported three acceptable rabbit developmental studies. With respect to the third rabbit developmental study, it stated (p.10):

> "In the third study, incidences of **reduced fecal output, soft/liquid feces, and blood on tray** were observed in the dams starting in the mid-dose group. This effect was accompanied by decreased body weight and food consumption. Increased incidence of late embryonic deaths, and post-implantation loss were also observed in the high-dose group. **Increased incidence of fetal cardiovascular variations,** primarily variations in the major blood vessels and the heart, was observed starting in the mid-dose group. This effect was accompanied with an increased incidence of **fetal cardiovascular malformations, primarily mostly interventricular septal defects**, in the high-dose group. The observation of cardiovascular malformations was considered **a serious effect** in this study although maternal toxicity was present at the same dose level. For a more detailed discussion of these malformations, please see document in PMRA#: 2310366]."

Although PMRA considered cardiovascular malformation to be a serious effect, it tempered this conclusion when it came to setting the endpoint. In PRVD 2015-01 PMRA states (p.17) "However, the concern regarding the serious nature of this effect was tempered by the presence of maternal toxicity at the same and lower dose levels in this study. Therefore, the Pest Control Products Act factor was reduced to three-fold when this endpoint was used to establish the point of departure."

This reduction of the importance placed on avoiding cardiovascular malformations (as well as foetal resorptions, skeletal deformities and delayed ossification noted on PRVD2015-01, pp 13-14) is unfathomable. It is well known by expectant mothers that exposures that may have no obvious effect on them may harm their unborn baby. With a long, sorry history of public health disasters such as thalidomide and diethylstilbestrol the PMRA contention that maternal adverse effects are tied to the importance of foetal harms, and that this merits *lowering* the margin of exposure is not consistent with the science. This amounts to an inappropriate reduction of the Pest Control Products Act Factor, and may be resulting in harms in farming communities. The reduction in the this factor is addressed further below.

Both epidemiological and animal studies conducted prior to and since PRVD2015-01 demonstrate developmental prenatal and postnatal toxicity in the young, and second-generation effects in both females and males. Thus, greater weight should be given to the line of evidence that glyphosate causes prenatal and postnatal toxicity in the young, and also supports the need to apply the ten-fold margin of safety and the full Pest Control Products Act Factor.

The ASTDR Toxicological Profile reported on developmental studies at pages 76 to 80 and, and provided a summary of its findings on developmental health effects at p. 6 as follows:

> Developmental Effects. Limited epidemiology studies provided suggestive evidence of associations between maternal preconception exposure to glyphosate and increased risk of spontaneous abortion (Arbuckle et al. 2001)[4] and parent-reported attention deficit disorder/attention deficit hyperactivity disorder (Garry et al. 2002). Depressed weight and increased incidence of unossified sternebrae were observed in gestation day (GD) 20 fetuses from rat dams treated with glyphosate technical by gavage at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e). In a study of rats exposed via the diet for 2 generations, up to 14–20% depressed pup body weight and/or body weight gain were noted at an estimated glyphosate technical dose of 3,134 mg/kg/day (EPA 1992a). In another 2-generation oral rat study, an estimated glyphosate technical dose of 1,234 mg/kg/day resulted in delayed preputial separation (EPA 2013a). A 3-generation study in Sprague-Dawley rats using only 25 mg/kg/day glyphosate technical found delays in puberty in F1 males and significant increases in organ system diseases in F2 and F3 rats of both sexes (Kubsad et al. 2019).

Recent epidemiological studies of pregnancy outcomes with glyphosate exposure

Parvez et al. (2018) reported in "Glyphosate Exposure in Pregnancy and Shortened Gestational Length: A Prospective Indiana Birth Cohort Study"[22] shorter gestation (length of pregnancy) was significantly correlated with glyphosate in maternal urine. Glyphosate was not detected in drinking water, but was detected in 93 percent of participants, with a detection limit of 0.1 ng/mL. Significantly higher levels were measured in women in rural areas (p=0.02).

Rappazzo et al., (2019) reported in "Maternal Residential Exposure to Specific Agricultural Pesticide Active Ingredients and Birth Defects in a 2003-2005 North Carolina Birth Cohort"[23] that "… atrial septal defects were positively associated with higher levels of exposure to glyphosate …"

Animal studies confirm effects of glyphosate exposure in utero.

A key study since PRVD2015-01 is the "Ramazzini 13-week pilot study"[24] , which showed that "both glyphosate and glyphosate formulated Roundup, at doses permitted in humans, including children and pregnant women, "significantly altered the microbiota diversity and resulted in prominent changes at multiple taxon in exposed pups."

Teleken *et al.* (2019) reported in "Glyphosate-based herbicide exposure during pregnancy and lactation malprograms the male reproductive morphofunction in F1 offspring"[25] that with addition of Roundup to the maternal drinking water during gestation, male mice exposed *in utero* experienced delayed testicular descent, 70% lower sperm count, and testicular morphological abnormalities.

Multigenerational reproductive harms

As discussed above, PMRA in its risk assessment looked at three, two-generation toxicity studies in rats to assess reproductive toxicity (PRVD p. 14), making the unscientific proposition that maternal toxicity would precede or accompany foetal harms.

Independent researchers examining other endpoints are finding important, significant adverse effects of low, transient exposures during F0 pregnancy. For example:

- A pioneering study of transgenerational effects in male rats, of a transient low exposure to glyphosate during initial pregnancy, was published by Kubsad *et al.* (2019) "Assessment of Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology."[26] They reported the greatest effects in F2 and F3 (i.e., grand- and great-grand- offspring), including prostate disease, obesity, kidney disease, ovarian disease, and parturition (birth) abnormalities, and that these were associated with differential regions of DNA methylation (an epigenetic effect).

- Gestational effects were followed up by Milesi et al. (2020), in "Perinatal exposure to a glyphosate-based herbicide impairs female reproductive outcomes and induces second-generation adverse effects in Wistar rats."[27] Noting global concerns of deleterious trends in reproductive health outcomes, including decreasing fertility, and increasing miscarriages, stillbirth, low birth weight and birth defects, they examined second-generation effects on fertility and pregnancy outcomes in dams that had been exposed *in utero* and concluded, "perinatal exposure to low doses of a GBH impaired female reproductive performance and induced fetal growth retardation and structural congenital anomalies in F2 offspring."

- Transgenerational effects of glyphosate exposure in utero were also reported in males in F1, F2 and F3, by Ben Maamar et al. (2020), "Epigenome-wide association study for glyphosate induced transgenerational sperm DNA methylation and histone retention epigenetic biomarkers for disease."[28] They examined inheritance following F0 maternal exposure, of prostate disease, kidney disease, obesity, and presence of multiple diseases, in an epigenome-wide association

study. Unique epigenetic signatures identified for each condition were carried forward in sperm from F1, to F2 and F3.

Health Risk Assessment Requires Assessment of New Risk - fungal diseases and cadmium contamination of food

Concerns regarding effects of pesticides on foods are typically restricted to contamination with the particular chemical and breakdown products. This is not the case for glyphosate, as this biologically potent chemical results in other effects that impact food quality. Use of glyphosate should trigger not only monitoring of the herbicide and degradates, it should also trigger more intense scrutiny of fungal infections and contamination with heavy metals.

Just as health effects of glyphosate result from secondary effects of the pesticide on the gut microbiome, the earth is similarly affected. Toxic mould contamination (e.g., *Fusarium spp.*) originates in the soil microbiome, and mould overgrowth may also be promoted by glyphosate. Use of the herbicide in agriculture is linked to higher levels of fungal disease species including *Fusarium* (toxic black mould that can rot plants, and render grains and other foods highly hazardous).[29,30]

Glyphosate also acts as a chelator and can mobilize toxic metals in the soil and facilitate their uptake by plants. Canadian commodities are also affected by cadmium contamination originating naturally in some soils and present at high levels in Canadian potash fertilizer. An industry website https://keepingitclean.ca urges Canadian producers to preserve markets and ensure that exports meet international standards for contaminants such as glyphosate. Until recently, the website also encouraged testing for cadmium. Canadian commodities have been returned from Europe, for not meeting European contaminant standards. High glyphosate, *Fusarium* and cadmium in Canadian commodities represent not only health hazards that require assessment, but also trade barriers with jurisdictions that have more restrictive, safer standards such as the E.U.

Reduction of the PCPA Factor without Scientific Rationale

The Pest Control Products Act factor (**PCPA Factor**) is set out in the PCPA for (among other things) the protection of infants and children, and it requires the application of a margin of safety for infants and children of 10 times the margin that would otherwise be applicable. The PCPA Factor is to be applied when the product is to be used around children (ie. around homes or schools) “to take into account pre- and post-natal toxicity”. Section 11(2)(b) of the PCPA sets this out. It states that the Minister shall, in evaluating the health risk associated with maximum residue limits for the pest control product:

> (b) in the case of a threshold effect, apply a margin of safety that is ten times greater than the margin of safety that would otherwise be applicable under subparagraph 7(7)(b)(ii) or 19(2)(b)(ii) in respect of that threshold effect, to take into account potential pre and post-natal toxicity and completeness of the data with respect to the exposure of, and toxicity to, infants and children, unless, on the basis of reliable scientific data, the Minister has determined that a different margin of safety would be appropriate.

Policy of the PMRA indicates the Pest Control Products Act sets a presumption in favour of the 10 fold margin of safety. PMRA indicates in Science Policy Note SPN2008-01 *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides* (29 July 2008) as follows:

> "The PMRA interprets the new PCPA provisions as requiring a presumptive application of the 10-fold factor for the protection of infants and children. In other words, the onus is on the PMRA to provide a reliable scientific rationale in those cases where the 10-fold PCPA factor is reduced….", (emphasis added)

The Conclusion of SPN2008-01 (at 18) is that deviations from application of the Pest Control Products Act factor require sound scientific justification:

> "It should be noted that deviations from this guidance would be considered on the basis of developments in science or risk assessment methodologies or changes in policy approach; however, such deviations would require sound scientific justification." (emphasis added)

Despite its policy, PMRA reduced the Pest Control Products Act factor from 10 to 3 in PRVD2015-01 in its consideration of prenatal or postnatal toxicity and reduced it from 10 to 1 in all other scenarios. It did so without pointing to any developments in science or risk assessment methodologies on changes in policy approach.

The explanation provided by PMRA for the reduction of the PCPA Factor from 10 to 3 was in the context of the discussion of the 'serious endpoint" found in the third rabbit developmental study discussed above. PMRA in PRVD2015-01 at 17 stated:

> "Overall, the endpoints in the young were well characterized. The increased incidence of fetal cardiovascular malformations noted in a rabbit developmental toxicity study was considered a **serious endpoint**. However, the concern regarding the serious nature of this effect was tempered by the presence of maternal toxicity at the same and lower dose levels in this study. Therefore, the Pest Control Products Act factor was reduced to three-fold when this endpoint was used to establish the point of departure. For all other scenarios, the Pest Control Products Act factor was reduced to one-fold since there were no residual uncertainties with respect to the completeness of the data, or with respect to potential toxicity to infants and children."

The tempering of the concern surrounding the "serious endpoint" is not justified, based on the approach outlined in SPN2008-01. In the description in SPN2008-01 of the consideration of pre-natal or post-natal toxicity it is stated (at 17):

> "If toxicity data indicate no prenatal or postnatal toxicity or the level of concern is low (and the data is considered complete), then the presumption for use of the 10-fold PCPA factor will be obviated with respect to the potential for prenatal and postnatal toxicity (i.e. the PCPA factor would be reduced to one-fold). If the level of concern is high, the 10-fold PCPA factor will be retained."

It is obvious the level of concern was "high"', given PMRA's characterization that cardiovascular malformation in the young rabbits were "serious", and, as such the 10-fold PCPA Factor should have been applied. The fact that there was also maternal toxicity does not detract from the seriousness of the toxicity to the fetuses; particularly when the focus of the analysis (as set out in SPN2008-01 and Subsection 19(2)(iii)(ii)) is whether there are indications of "prenatal or postnatal toxicity" "with respect to the exposure of, and toxicity to, infants and children". There was no evidence of developments in science or risk assessment methodologies or changes in policy, or evidence that the young had to be more sensitive than the mother to toxicity. The rationale for the factor is protection of infants and children, not "protection of infants and children only if they are affected more than the mother".

Moreover, in the study, the young showed increased incidence of fetal cardiovascular malformations, whereas the dams exhibited toxicity, not malformations. The argument that the young must show more pronounced sensitivity than the mother presumes that the sensitivity be of the same type. In this instance, the exhibited sensitivities were different.

The explanation provided by PMRA for the reduction of the PCPA Factor from 10 to 1 in all other instances was simply that there were "no residual uncertainties with respect to the completeness of the data". However the presumption is the "application of the 10-fold factor for the protection of infants and children", and this is not to be changed unless there are developments in science or risk assessment methodologies or changes in policy approach. PMRA did not provide any information on such developments or changes that would rebut the presumption. Based on the foregoing, PMRA acted without justification in reducing the PCPA Factor from 10 to 1 and not applying a reduction in the toxicological endpoints by a factor of 10 in its dietary risk assessment.

The endpoints for the dietary risk assessment, with application of the 10-fold factor, should be revised to the following, calculated as follows:

Acute Reference Dose General Population (Excluding Females 13-49 Years of Age):

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw/day}}{1000} = 0.1 \text{ mg/kg bw of glyphosate}$$

Acute Reference Dose Females 13-49 years of age

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{150 \text{ mg/kg bw/day}}{1000} = 0.15 \text{ mg/kg bw of glyphosate}$$

Acceptable Daily Intake General Population

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{32 \text{ mg/kg bw/day}}{1000} = 0.032 \text{ mg/kg bw of glyphosate}$$

The revisions to the endpoints would result in exceedances of the Acute Reference Doses and the Acceptable Daily Intake at all percentiles, for all populations.

The DEEM aggregate acute risk assessment as set out in the Monsanto DEA indicates the exposure varies between 12.87% (Males 50-99) and 46.16% (children 1-2) of the aRfD at the 95th percentile. This

would change to a range of 128.7% to 461.6% of the aRfD, representing significant exceedances, at the 95th percentile.

These values at the 99.9th percentile in the Monsanto DEA vary from a range of 30.13% (Males 50-99) and 322.06 (children 1-2) of the aRfD. The revision to the aRfD would change the values to a range of 301.30% (Males 50-99) and 3220.6 % (children 1-2) of the aRfD.

The DEEM aggregate chronic risk assessment as set out in the Monsanto DEA indicates the total exposure varies between 19.7% (Adults 50-99) and 75% (children 1-2) of the ADI. This would change to a range of 197% to 750% of the ADI, representing significant exceedances.

Comments on other Components of a Health Risk Assessment

Did Not Conduct an Occupational or Residential Exposure Assessment

A health risk assessment requires a dietary, occupational and residential exposure assessment (SPN2003-02 p. 9, SPN 2014-01 p. 1). PMRA did not conduct an occupational or residential exposure assessment. Although the Evaluation Report spoke to "Health Assessments" in one section, in that section PMRA merely indicated that it had reviewed field trial data from field trials in Canada and the US for dry peas and dry beans and tree nuts, and updated the dietary exposure assessment.

PMRA stated in the Evaluation Report that toxicology and occupational exposure assessments were not required. Similarly, the Monsanto DEA indicates that aggregate assessments of dietary and dermal exposures from residential and "pick-your-own" activities, was not updated since PRVD2015-01 since "no major changes to the Canadian domestic use pattern have taken place since the last assessment was conducted during the re-evaluation (refer to the PVD2015-01)".

There is no basis for stating that an occupational exposure assessment is not required. The exposure of farmers and applicators to the product will be significantly increased, as well as bystanders and those subjected to drift, so a new assessment taking into account higher exposure values is required for a proper assessment of health risks.

The scientific literature since PRVD2015-01 shows risks of concern arising from occupational and bystander exposure, some of which provide evidence on exposure pathways and new modelling techniques.

Did Not Conduct an Aggregate Risk Assessment

Drinking Water

Drinking water is of the Factors set out in Section 11 of the PCPA, which requires that the Minister assess "available information" on "dietary exposure and exposure from other non-occupational sources, including drinking water and use in and around homes and schools", as well as "the different sensitivities to pest control products of major identifiable subgroups, including pregnant women, infants, children, women and seniors".

New information and estimated environmental concentrations of glyphosate in drinking water were not assessed in the health risk assessment of PMRA. The Monsanto DEA indicates that in the context of the submission on import commodities, "new estimated environmental concentrations (EECs) in drinking water were not remodeled as the pesticide will not be used in Canada and will not contribute to

potential residues in drinking water sources" (p.14), and indicated the drinking water values on file used in PRVD2015-01 and RVD2017-01 would be used.

Given that MRLs for glyphosate proposed in the Submission Report are being proposed for both domestic and import use, as discussed, new EECs in drinking water are required. The previous assessment included examination of a small reservoir and a prairie dugout (which was not modelled), and used data for drinking water sources in the US, so was not informative.

PMRA in PRVD-2015 (p. 235) indicates glyphosate is found in drinking water coming from surface water. The literature indicates the concentration of glyphosate in water has increased significantly since the May 2013 Environmental Assessment Directorates modelling of drinking water that was used for PRVD2015-01. For example, the 2022 report of Giroux for Quebec[5] notes (at pages 13 and 68):

> "Detection of glyphosate and its degradation product, AMPA, has increased significantly [in Quebec rivers] over the years. Glyphosate is detected in almost all samples (98.9%) and AMPA is now detected in 93.3% of samples on average for the period 2018-2020, which represents an increase compared to the period 2015- 2017 where it was detected in 79.7% of the samples.
>
> Glyphosate concentrations [in Quebec rivers] increased significantly between 2005 and 2020. This increase mainly occurred from 2005 to 2010 and there seems to be a stabilization for the period from 2010 to 2020. However, AMPA concentrations are on the rise in the four rivers. The scientific literature suggests that a high ratio of glyphosate/AMPA concentrations (more glyphosate than AMPA) indicates rapid transport to the watercourse and a low ratio (more AMPA than glyphosate) would indicate slow transport.

Sensitivities of Subpopulations

The sensitivities of children, women, vegetarians and minorities to glyphosate products is particularly important.

Children consume a large amount of breakfast cereal, and consumer and public interest groups have consistently shown high levels of glyphosate in North American breakfast cereals. The Environmental Working Group (EWG) conducted three sets of testing of children's food including breakfast cereals, in July and October of 2018, and May of 2019, and found all the products except 4 exceeded levels considered safe by EWG (.16 ppm) after applying margins of safety. The highest levels were in Cheerios Toasted Whole Grain Oat Cereal (at .729 ppm) and Honey Nut Cheerios Medley Crunch (at .833 ppm). Nature Valley Granola bars had more than .5 ppm.

Cereals and legumes are consumed by health conscious people, vegetarians, and legumes are consumed by many minorities as a basic diet protein. The diets consumed by these people is being inordinately affected by glyphosate contamination and the risks to these subpopulations should be assessed.

The presence of glyphosate in these food is being found by consumer and advocacy groups. The Detox Project recently reported on The Poison in Our Daily Bread: Glyphosate Contamination Widespread in Essential Foods, and found that healthier foods and plant-based staplfto es contain high levels of

[5] GIROUX, I. (2022). Présence de pesticides dans l'eau au Québec : Portrait et tendances dans les zones de maïs et de soya – 2018 à 2020, Québec, ministère de l'Environnement et de la Lutte contre les changements climatiques, Direction de la qualité des milieux aquatiques, 71 p. + 15 ann.

glyphosate, due to the practise of preharvest use of glyphosate. It is a fulsome report that discusses the risks of preharvest spraying, and also presents findings relevant to points made above, that "glyphosate-based herbicides cause genotoxicity, alteration of the intestinal microbiome as well as reproductive and developmental effects in both male and female rats, at the currently considered safe level in the U.S. of 1.75 mg/kg/ b w day." Mom's Across America recently reported that wheat coming from Canada was contaminated with high levels of glyphosate.

The Entire Pest Control Product is More Toxic But Was Not Assessed

The PCPA defines "Pest Control Product" such that it could be understood as a product consisting of an active ingredient, formulants and contaminants (**Entire Product**), or just the active ingredient. The health risk assessment conducted by PMRA examined just the active ingredient, Glyphosate, and not the Entire Product.

This is problematic for two reasons. First, humans are exposed to the Entire Product, not just the active ingredient, so assessment of anything less than what humans are exposed to in the "real world" can not give rise to a reasonable certainty that no harm will arise from exposure. Second, the recent science has shown that there are major concerns with the formulants and contaminants that are combined with the active ingredient.

It is well established that formulant and contaminants can be toxic in their own right, and cause the Entire Product to be more toxic than the stated active ingredient alone. This has been shown, for example, in Mesnage R, Defarge N, Spiroux de Vendômois J, Séralini GE. Major pesticides are more toxic to human cells than their declared active principles. Biomed Res Int (2014) 014:179691.10.1155 /2014/179691.

Moreover, the Entire Product can contain heavy metals and other harmful substances, as shown in, for example, N.DefargeaJ.Spiroux de VendômoisbG.E.Séralini. Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides. https://doi.org/10.1016/j.toxrep.2017.12.025.

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