GLYPHOSATE

Summary of the Pest Management Regulatory Agency
Proposed Re-evaluation Decision
http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_prvd2015-01/prvd2015-01-eng.php
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Executive Summary

Human Health and Safety
Overall Summary

The toxicology database submitted for glyphosate is adequate to define the majority of toxic effects that may result from exposure. The risk assessment carried out by the PMRA protects against toxic effects observed in laboratory studies by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in the animal tests.

Dietary Risk

There were no dietary risk concerns from the acute and chronic dietary risk assessments (food and drinking water) for the general population and all population subgroups, including infants, children, teenagers, adults and seniors.

Non-Occupational Risk

Risks to residential applicators for all residential label uses, and post application risk, are not of concern. There is no risk of concern for bystanders entering treated sites.

Occupational Risk

Risk estimates associated with mixing, loading and applying activities for all commercial label uses are not of concern. Post application risks for workers were not of concern. A Re-Entry Interval (REI) of 12 hours is required for all agricultural post application activities.

Aggregate Risk

There were no risks of concern from aggregate exposure to glyphosate from food, drinking water and residential uses.

Polyethoxylated Tallow Amines (POEA)

No risks of concern were identified, provided end-use products contain no more than 20% POEA by weight. All Canadian glyphosate products meet this threshold.

Environmental Risk

Available studies indicate that in the natural environment, glyphosate is non-persistent to moderately persistent in soil and water and produces one major transformation product in soil and water, aminomethyl phosphonic acid (AMPA),

which is non-persistent to persistent in the environment. Carryover of glyphosate and AMPA into the next growing season is not expected to be significant. Glyphosate and AMPA are expected to be immobile in soil and are unlikely to leach to groundwater. Glyphosate is very soluble in water and non-volatile and is expected to partition to sediment in aquatic environments. Glyphosate and AMPA are unlikely to bioaccumulate.

Some glyphosate formulations include the surfactant POEA, which is non-persistent to slightly persistent in the environment and is toxic to aquatic organisms. In general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine organisms than formulations that do not contain POEA. Given that the components of POEA are easily broken down and that it is not persistent in soil and water, significant bioaccumulation under field conditions is unlikely.

In the terrestrial environment the only area of risk concern identified from the available data was for terrestrial plants and therefore spray buffer zones are required to reduce exposure to sensitive terrestrial plants. Glyphosate formulations containing POEA may pose a risk to freshwater invertebrates, freshwater plants and marine/estuarine invertebrates. Glyphosate formulations that do not contain POEA may pose a risk to freshwater algae only. Glyphosate technical grade active ingredient is toxic to estuarine/marine fish. Hazard statements and mitigation measures (spray buffer zones) are required on product labels to protect aquatic organisms.

Due to its rapid dissipation and low toxicity, the transformation product AMPA is not expected to pose a risk to terrestrial and aquatic organisms based on proposed application rate of glyphosate.

Value

Glyphosate is an important herbicide for Canadian agriculture as well as for weed control in non-agricultural land management.

The PMRA re-evaluation process

In the US and Canada, pesticide registrations are re-evaluated on a 15 year cycle; the re-evaluations are carried out on a cooperative basis. The PMRA has estimated that approximately 90% of all pesticide active ingredients have undergone a re-evaluation.

The last re-evaluation of glyphosate by the US EPA was in 1993. In 2010, Health Canada published a re-evaluation work plan for glyphosate outlining the focus of this re-evaluation and indicating that the PMRA is working cooperatively with the United States Environmental Protection Agency on the re-evaluation of glyphosate.

As part of this re-evaluation, the effect of Polyethoxylated Tallow Amines (POEA), an emulsifier used in many glyphosate formulations, and the metabolite and transformation product aminomethylphosphonic acid (AMPA) are also included. The PMRA released its 330 pg re-evaluation on April 13. The US EPA re-evaluation is expected in June.

What Does Health Canada Consider When Making a Re-evaluation Decision?

Health Canada's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information.

What Decision did the PMRA propose for Glyphosate ?

Following a lengthy re-evaluation of the safety of glyphosate, **Health Canada's Pest Management Regulatory Agency (PMRA), proposed continued registration of products containing glyphosate for sale and use in Canada**. As a condition of the continued registration of various glyphosate uses, the PMRA has proposed new risk reduction measures for glyphosate end-use products registered in Canada. The PMRA has not requested any additional data at this time.

What Did Health Canada Consider When Making Its Re-evaluation Decision?

Health Canada considers potential risks as well as the value of pesticide products to ensure they meet modern standards to protect human health and the environment. The re-evaluation process draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information. In the case of the glyphosate re-evaluation, the PMRA had indicated that it would be working cooperatively with the US EPA. **As part of this re-evaluation, the PMRA also considered the effect of polyethoxylated tallow amine (POEA) surfactants, which are used in many glyphosate formulations, and the metabolite and transformation product of glyphosate - aminomethylphosphonic acid (AMPA).**

What Is Glyphosate?

Glyphosate is a non-selective herbicide registered for post-emergence control of a wide spectrum of weeds including annual and perennial broadleaf and grassy weeds, weedy trees and brush. It is registered under various forms including glyphosate acid, glyphosate isopropylamine or ethanolamine salt, glyphosate mono-ammonium or diammonium salt, glyphosate potassium salt and glyphosate dimethylamine salt. The PMRA have noted that another form of glyphosate,

glyphosate trimethylsulfonium salt, was voluntarily discontinued by the registrant and therefore is not included in the current re-evaluation.

Once absorbed by the plant, **glyphosate blocks the shikimic acid pathway** that converts simple carbohydrate precursors derived from glycolysis and the pentose phosphate pathway to aromatic amino acids and many other important plant metabolites. **The shikimic acid pathway does not exist in humans.**

In Canada, a total of 169 products contain glyphosate, including 19 technical grade active ingredients, 19 manufacturing concentration, 97 commercial class end-use products and 34 domestic class end-use products. Although glyphosate is registered in various forms, there are no differences in efficacy and toxicity end-points among glyphosate forms. Glyphosate is registered for use in forests and woodlots, industrial oil seed crops and fibre crops, terrestrial feed crops, terrestrial food crops, industrial and domestic vegetation control non-food sites, outdoor ornamentals and turf.

Glyphosate is the largest selling herbicide, by volume, in the world. Glyphosate products are formulated as solutions, pastes or tablets and can be applied using ground or aerial equipment. Some special application techniques are also used.

Health Considerations
Can Approved Uses of Glyphosate Affect Human Health?

The PMRA have concluded that products containing glyphosate acid are unlikely to affect human health when used according to label directions.

Potential exposure to glyphosate may occur through the diet (food and water), when handling and applying the products containing glyphosate, or by entering treated sites. When assessing health risks, two key factors are considered by the PMRA: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for registration. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when glyphosate products are used according to label directions.

In laboratory animals, glyphosate was of low acute oral, dermal and inhalation toxicity. Glyphosate did not cause skin irritation or an allergic skin reaction. It was severely irritating to the eyes. The PMRA also considered numerous other animal toxicity tests, as well as numerous peer-reviewed studies from the published scientific literature, which assessed the potential of glyphosate to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The PMRA risk assessment

approach ensures that the level of exposure to humans is well below the lowest dose at which any effects occurred in animal tests.

A number of published epidemiology studies were reviewed by the PMRA for incorporation into the hazard assessment of glyphosate. The majority, however, lacked adequate characterization of glyphosate exposure, rendering them of limited use for supplementing the hazard assessment. A prospective cohort study of licensed pesticide applicators in Iowa and North Carolina, known as the Agricultural Health Study (AHS), examined the relationship between glyphosate exposure and cancer incidence. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes studied. There was a suggested association with multiple myeloma incidence. However, a number of confounding factors (for example, the lack of consideration of exposure to UV radiation from sunlight) rendered these findings inconclusive and chance occurrence could not be ruled out. The authors recommended this should be followed up as more cases occur in the AHS (see addendum included in this summary report).

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 genotoxicity assays, as well as the large body of epidemiological information**, the PMRA concluded that the overall weight of evidence indicates that glyphosate is unlikely to pose a human cancer risk. The PMRA noted that this conclusion is consistent with all other pesticide regulatory authorities world-wide**, including the most recent, ongoing comprehensive re-evaluation by Germany (Rapporteur Member State for the European Union) that was published for public consultation in 2014[1].

The PMRA has reviewed the recent hazard classification of glyphosate by the International Agency for Research on Cancer (IARC) as a "probable human carcinogen". The determination of risk, however, is not solely driven by the hazard profile but is also a function of the potential exposure to the pesticide. For this reason, both the hazard and exposure potential must be considered together when performing a human health risk assessment for a pesticide, since **an identified hazard may be offset by the fact that the potential for human exposure is considered to be sufficiently low so as not to pose a risk of concern to human health. The PMRA noted that the level of human exposure with glyphosate uses, which determines the actual risk, was not taken into account by IARC. The PMRA also noted that pesticides are registered for use in Canada only if the level of exposure to Canadians does not cause any harmful effects, including cancer (see addendum included in this summary report).**

[1] http://dar.efsa.europa.eu/dar-web/provision

Residues in Food and Water

Potential acute and chronic dietary exposures to glyphosate were estimated from residues of glyphosate and its metabolites in both treated crops and drinking water. Exposure to different subpopulations, including children and women of reproductive age, were considered in the assessment.

The PMRA concluded that dietary risks from glyphosate residues in food and water are not of concern for human health in any subpopulation.

Risks in Residential and Other Non-Occupational Environments

Residential exposure may occur from the application of products containing glyphosate to residential lawns, and turf (including golf courses). Residential handler exposure would occur from mixing, loading and applying domestic-class glyphosate products. These products can be applied as a liquid by a manually pressurized hand wand, backpack, sprinkler can and ready-to-use sprayer.

Residential post application exposure may occur while performing activities on treated areas. Treated areas include areas treated by residential handlers as well as residential areas treated by commercial applicators. Exposure would be predominantly dermal. Incidental oral exposure may also occur for children (1 to < 2 years old) playing in treated areas.

Following an extensive review of these uses, the PMRA concluded that non-occupational risks are not of concern when products are used according to label directions.

Occupational Risks from Handling Glyphosate

The PMRA concluded that occupational risks to handlers for all use scenarios are not of concern.

The Polyethoxylated Tallow Amine Emulsifier (POEA) Used in Many Glyphosate Products

POEA is a family of several compounds that are used as surfactants in many glyphosate products registered in Canada. **The PMRA concluded that no human health risks of concern were identified, provided that end-use products contain no more than 20% POEA by weight. The PMRA confirmed that all of the currently registered glyphosate end-use products in Canada do not exceed this limit.**

Environmental Considerations

Glyphosate can enter soil and surface water. Glyphosate breaks down in soil and water and is not expected to persist for long periods of time. Glyphosate produces one major transformation product in soil and water, aminomethyl phosphonic acid (AMPA), which can persist in the environment. Carryover of glyphosate and AMPA into the next growing season is not expected to be significant. **Glyphosate and AMPA are not expected to move downward through the soil and are unlikely to enter groundwater.**

Glyphosate dissolves readily in water but is expected to move into sediments in aquatic environments. Glyphosate is not expected to enter the atmosphere. **Glyphosate and AMPA are unlikely to accumulate in animal tissues.** Certain glyphosate formulations include a surfactant composed of POEA compounds. **At high enough concentrations, POEA is toxic to aquatic organisms but is not expected to persist in the environment.**

While, in general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine organisms than formulations that do not contain POEA, they do not pose an unacceptable risk to the environment when used as directed on the label.

In the terrestrial environment the only area of risk concern identified from the available data **was for terrestrial plants and therefore spray buffer zones are required to reduce exposure to sensitive terrestrial plants.**

Glyphosate formulations pose a negligible risk to freshwater fish and amphibians, but may pose a risk to freshwater algae, freshwater plants, marine/estuarine invertebrates and marine fish if exposed to high enough concentrations. Hazard statements and mitigation measures (spray buffer zones) are required on product labels to protect aquatic organisms.

When used according to proposed label directions, glyphosate products do not pose an unacceptable risk to the environment. Labeled risk-reduction measures mitigate potential risks posed by glyphosate formulations to non-target plants and freshwater/marine/estuarine organisms**.**

Toxicity Studies on the Metabolite Aminomethylphosphonic Acid (AMPA)

Overall, based on the available toxicity studies, AMPA was considered of no greater toxicological concern than glyphosate. Although no repeated dose toxicity studies were available for glyphosate metabolites resulting from genetically modified organism (GMO) crops (in other words, N-acetylglyphosate and N-acetyl AMPA), these glyphosate metabolites resulting from GMO crops were not considered to be of a greater toxicological concern than the parent compound,

glyphosate, based on an assessment carried out by the European Food Safety Authority.

Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to glyphosate from potentially treated imported foods is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). Dietary risk is then determined by consideration of the combination of the exposure and the toxicity. High toxicity may not indicate high risk if the exposure is low. Similarly, a pesticide with low toxicity may pose a high risk if there is high exposure. The acute dietary risk was calculated considering the highest ingestion of glyphosate that would be likely on any one day, using food consumption and food residue values.

The PMRA approach is to compare dietary exposures to reference toxicology values. When human exposure falls below toxicology reference values, the exposure is not considered to pose a risk to the target population. The PMRA concluded that the acute exposure estimate (exposure over a single day) at the 95th percentile for females 13-49 years old is 31% of the Acute Reference Dose (ARfD) and therefore is not of concern. Acute exposure estimates at the 95th percentile for all other population subgroups, other than females 13-49 years old, range from 12% to 45% of the ARfD and therefore are also not considered of concern by the PMRA.

Similarly, **the chronic exposure (daily exposure over a lifetime) estimate for the general population is not considered of concern by the PMRA**. Exposure estimates for population subgroups range from 20% to 70% of the toxicological "safe" level of exposure (Acceptable Daily Intake or ADI) and, therefore, are not of concern. The PMRA also considered a wide range of other potential sources of exposure, including occupational, non-occupational and residential use scenarios both during mixing, loading and application of glyphosate as well as post application, including lawn and turf. **Importantly, depending on the use scenario and potential for exposure, the PMRA assessment considered exposure in very young children, children, youths and adults. The PMRA did not identify any concerns associated with any use scenario for any population subgroup.**

Incident Reports Related to Human Health

Since April 2007, registrants have been legally required to report incidents to the PMRA that include adverse effects to the health of Canadians and to the environment. Information about the reporting of pesticide incidents can be found on the PMRA website. The PMRA searched and reviewed incident reports for the active ingredient glyphosate. As of January 2014, the PMRA had received 71 human and 167 domestic animal incident reports involving glyphosate.

A total of 75 individuals were affected in the human incidents. In almost half of these incidents, the described effects were considered to be associated with the reported pesticide exposure. Major incident reports involving glyphosate occurred mainly in the United States as a result of accidental ingestion. Other highly acutely toxic active ingredients (such as diquat and paraquat) were also noted in these incidents. Therefore, **any adverse effects could not be attributed specifically to glyphosate. Non-serious incidents, which included a prevalence of eye and skin irritation effects, occurred as a result of activities associated with application. Commercial class products were frequently identified in these incidents.**

Overall, the reported symptoms in animals were clinical signs of toxicity such as vomiting. Contact with a treated area and ingestion of vegetation treated with a product containing glyphosate were commonly noted as activities leading to exposure in animal incidents.

The PMRA has not required any label changes as a result of these incident reports.

Impact on the Environment

The environmental assessment was conducted based on data and information from registrants as well as from other regulatory agencies. Additional relevant data from published and unpublished scientific literature and monitoring data from federal and provincial governments were also considered.

Glyphosate and AMPA are not expected to bioaccumulate in aquatic and terrestrial organisms due to their low octanol-water partition coefficients. Certain surfactants found in glyphosate formulations, that are derived from POEA compounds (mixture of 100 discrete tertiary amine molecules) may have the potential for bioaccumulation. However, given that the components of these compounds are easily broken down and that they are not persistent in soil and water, significant bioaccumulation under field conditions is unlikely.

The surfactant POEA is expected to be non-volatile, non-persistent in soil and water and immobile in soil and sediment. It is not likely to leach to groundwater due to rapid microbial transformation and strong adsorption to soil particles.

Earthworms, Birds, Bees and Mammals

Acute and chronic studies indicate that glyphosate is not toxic to earthworms and the resulting risk quotients based on the maximum application rate indicate that glyphosate is not expected to pose a risk to earthworms.

Glyphosate is not acutely toxic (contact and oral) to adult bees and risk quotients indicate that **glyphosate is not expected to pose a risk to adult bees.** Chronic bee toxicity studies were not available for review; however, the PMRA noted that chronic effects are not expected based on the mode of action and the lack of effects in acute toxicity studies with adult bees. **The PMRA concluded that this evidence, in combination with the absence of bee incident reports associated with the long history of use in Canada and foreign countries, indicates that glyphosate is unlikely to pose significant risks to honeybees.**

The PMRA has conducted a tiered assessment of the risks to birds, progressing from a conservative screening assessment to a more refined assessment. In the vast majority of studies, no toxic effects were reported. Consequently, a very conservative assessment was conducted using risk quotients generated using the highest concentration tested even though in all but one case, no toxic effects were observed. This assessment identified only very minor concerns and concluded that the risk to birds from acute oral, dietary and reproduction exposure to glyphosate and its formulations is expected to be low. **The absence of incident reports for birds related to the use of glyphosate supports this conclusion. The PMRA has not required bird hazard statements on glyphosate product labels**.

Toxic effects were reported in only a few of the available studies conducted with mammals and these effects were observed only at very high doses. A tiered assessment of the risks to mammals progressing from a conservative screening assessment to a more refined assessment was conducted. This assessment concluded that the risk to mammals from acute oral and reproduction exposure to glyphosate and its formulations is expected to be low. If any, acute risks to mammals would be restricted to on-field exposure of only a few guilds (herbivores and perhaps insectivores). **No reproductive risks to mammals are expected from the use of glyphosate.** This conclusion is supported by the absence of incident reports for mammals related to the use of glyphosate. Mammalian hazard statements are not required on glyphosate product labels.

Risk to Non-target Terrestrial Plants

Glyphosate is a broad-spectrum herbicide and as such toxicity to susceptible non-target plants is expected if exposed to sufficiently high concentration. **The PMRA risk assessment for non-target terrestrial plants identified some areas of potential risk. Consequently buffer zones are required on glyphosate product labels, both those with and without the surfactant POEA, to minimize exposure to non-target plants.**

Transformation Product (AMPA)

Earthworms and birds were the only terrestrial organisms tested with the transformation product AMPA. Since AMPA is mainly formed in soils through biological processes, has a low log *K*ow (-2.36 to -1.63) and binds tightly to soil particles, exposure and risk to mammals and foliage dwelling arthropods is expected to be negligible. **To date, no ecotoxicological incidents have been reported concerning AMPA. As such no additional studies are required by the PMRA at this time.**

Risks to Aquatic Organisms

Glyphosate can enter water bodies and expose non-target aquatic organisms through runoff or via spray drift. The PMRA conducted an aquatic risk assessment following a tiered approach with a very conservative screening assessment followed by refinements if concerns were identified at the screening level. **Overall there are few risks of concerns for aquatic organisms with the exception of aquatic plants and some marine invertebrates and these areas of concern were mainly identified with formulations containing the surfactant POEA.** The surfactant POEA tested identified concerns for freshwater and marine/estuarine invertebrates and freshwater fish, confirming the international scientific consensus that POEA added to glyphosate increases the environmental risk to these organisms.

The transformation product AMPA is not toxic to aquatic organisms.

Value of Glyphosate

Glyphosate plays an important role in Canadian weed management in both agricultural production and non-agricultural land management and is the most widely used herbicide in Canada.

Value to Canadian Agriculture

• Due to its broad and flexible use pattern and its wide weed control spectrum, **it is the most widely used herbicide in several major crops grown in Canada such as canola, soybean, field corn and wheat. It is also one of only a few herbicides regularly used in fruit orchards such as apple.**

• **It is the essential herbicide for use on the glyphosate tolerant crops** (GTCs) including canola, soybean, corn, sweet corn and sugar beet. The combination of GTCs and glyphosate has been adopted as an important and common agricultural production practice in Canada.

It is identified by growers (in the Canadian Grower Priority Database [version 22, August 2011]) as a priority for 17 new uses relating to 17 commodities: almond, bluegrass, kentucky bluegrass, bromegrass, canary seed, creeping red fescue, fescue,

bermuda grass, pearl millet (grain), orchard grass, peanut, pecan, ryegrass, soybean, sunflower, timothy and wheatgrass.

• Among all herbicides registered, glyphosate has the broadest range of use sites because it can be used on all crops when applied prior to planting. In addition, it has the widest weed control spectrum including annual and perennial weeds, weedy trees and brush.

• Compared to other non-selective herbicides, it controls weeds of various sizes as well as the roots of these weeds since glyphosate is translocated throughout the plant.

• Glyphosate can be tank-mixed with many residual herbicides to broaden the weed spectrum and extend the duration of weed control thus decreasing the number of herbicide applications while maximizing yield and lowering fuel and energy consumption.

• Glyphosate has a wide application window including pre-seeding, after seeding (prior to crop emergence), in-crop, pre-harvest and post-harvest, allowing a flexible and effective weed management program. When applied prior to seeding, application does not delay the seeding step due to its non-residual activity, therefore increasing flexibility for farming practices while providing a clean start for the new crop.

Glyphosate can also be applied in-crop as a post emergence treatment in conventional crops either as spot treatment or with wiper and wick application to control weeds taller than crops, which otherwise are impossible to control with other herbicides.

The pre-harvest application of glyphosate provides additional benefits to growers as it functions both as a harvest management and a desiccation treatment: equalizing the ripening or advancing the ripening process in uneven crops to achieve an earlier and more uniform harvest, lowering harvested grain seed moisture content, and increasing combine harvester efficiency. As compared to alternative crop desiccators such as diquat, glufosinate and carfentrazone, glyphosate also controls perennial weeds and can be used in a wider range of crops.

Post-harvest stubble treatment with glyphosate allows reduced or zero tillage, which has facilitated the adoption of conservation agriculture, where appropriate, thus reducing soil erosion, improving soil structure and retaining soil moisture as well as providing other benefits such as reduced tractor and fuel use.

Value to Non-agricultural Land Management

Glyphosate is also an important weed control tool in non-agricultural land management for these reasons:

• Due to its flexible use pattern and broad weed control spectrum, it is the most widely used herbicide in forestry. It can be applied at various stages in the forest regeneration cycle including site preparation, conifer release and stand thinning stages. Compared to alternative herbicides such as phenoxy, sulfonylnurea and triclopyr, glyphosate controls a wider range of weeds. Special application methods such as cut stump or injection treatment allow for year round application.

• It is also one of the widely used herbicides for pasture renovation, around structures on farms, amenity and industrial areas, and along rights-of-way.

• It is an effective tool for the control of many invasive weed species and for the control of toxic plants such as poison ivy.

For some specialty or minor use crops, glyphosate provides specific selective weed control techniques (weed wipers, shrouded sprayers and stem injection) where in many cases selective use of glyphosate is the only method of weed control possible or remaining in pasture and rangeland, vegetables, fruit crops and for the control of invasive weeds among desirable plants/trees.

Glyphosate has a unique mode of action and is the only molecule that is highly effective at inhibiting the enzyme EPSP of the shikimate pathway. It plays a role in delaying herbicide resistance development in weeds when used in rotation or combination with active ingredients from other herbicide site of action groups. However, the current Canadian agricultural production system relies heavily on glyphosate, resulting in more and more occurrences of glyphosate-resistant weeds. Kochia, Canada fleabane, giant ragweed and common ragweed are examples of such resistant weeds reported in Canada. These glyphosate-resistant weeds affect the efficacy and broader value of glyphosate. In order to prevent or delay the development of glyphosate-resistant weeds, it is crucial to maintain diversity in weed management practices.

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Addendum : commentary by Leonard Ritter

On March 20, 2015 the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, classified glyphosate as a "probable human carcinogen". This designation was in sharp contrast to assessment of the carcinogenicity of glyphosate by the world's most prominent regulatory authorities. The goal of IARC assessments is to assess carcinogenic hazards from occupational, environmental, and lifestyle exposures and agents, thus providing an essential step in the societal decision-making process to identify and then control carcinogenic hazards. Carcinogenic hazard identification refers to an assessment of whether an agent causes cancer. Hazard identification does not predict the magnitude of cancer risks under specific conditions; this can be determined only with appropriate exposure-response information

The carcinogenicity of glyphosate has been widely reviewed prior to the recent IARC classification . In its 1993 re-registration of glyphosate, EPA concluded, "Based on the results of its reregistration review, EPA has concluded that all registered uses of glyphosate are eligible for re-registration. The Agency has classified glyphosate as a Group E carcinogen (signifies evidence of non-carcinogenicity in humans). In 2000, Williams et al [2]concluded that glyphosate did not demonstrate any tumorigenic potential. Accordingly, it was concluded that glyphosate is noncarcinogenic. In 2004, the Joint WHO/FAO Expert Meeting on Pesticide Residues concluded that administration of glyphosate produced no evidence of a carcinogenic response to treatment in rats[3]. In 2005, scientists working with the US Agricultural Health Study (AHS) concluded that glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes which they studied. There was a suggested association with multiple myeloma incidence, which the authors suggested should be followed up as more cases occur in the AHS[4]. This suggestion was followed up and in 2015. Sorohan concluded that there were no statistically significant trends for multiple myeloma risks in relation to reported cumulative days (or intensity weighted days) of glyphosate use in the AHS[5]. In 2012, Mink et al concluded that the currently available epidemiologic literature on glyphosate and cancer provides no evidence of a consistent pattern of positive associations that would be indicative of a causal relationship between any site-specific cancer and exposure to glyphosate[6]. In 2013, the US EPA concluded that glyphosate does not

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[2] Willams et al. Safety Evaluation and Risk Assessment of the Herbicide Roundup1 and Its Active Ingredient, Glyphosate, for Humans. 2000

[3] WHO/Joint Meeting on Pesticide Residues: Glyphosate, 2004

[4] *DeRoos et al. Cancer Incidence Among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study. 2005.*

[5] *T. Sorohan. Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data. 2015.*

[6] *Mink et al. Epidemiologic studies of glyphosate and cancer: A review. 2012*

pose a cancer risk to humans[7]. In 2015, the EU concluded that laboratory studies indicated that glyphosate did not pose a risk of carcinogenicity and further noted that epidemiological studies in the whole did not provide evidence of carcinogenicity in humans [8] .

The reaction to the recent IARC classification of glyphosate has been swift and consistent. On April 1, 2015, the US EPA indicated that it had reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. The US EPA concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. On March 23, 2015 the German risk assessment authorities noted that they had reviewed over 30 epidemiological studies and on this basis they came to the overall assessment that there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer. On April 13, 2015, the Pest Management Regulatory Agency of Health Canada noted the recent IARC WHO hazard classification for glyphosate as "probably carcinogenic to humans". The PMRA went on to note that a hazard classification is not a health risk assessment. The PMRA concluded that the level of exposure, which determines the actual risk, was not taken into account by IARC. The PMRA re-affirmed that pesticides are registered in Canada only if the level of exposure to Canadians does not cause any harmful effects, including cancer.

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[7] *Federal Register / Vol. 78, No. 84 / Wednesday, May 1, 2013 / Rules and Regulations*
[8] Renewal Assessment Report. Rapporteur Member State : Germany. January 29, 2015 on behalf of the EU.