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MONSANTO COMPANY

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

Case No. CGC-16-550128

Exhibit 1018 to 1020 to

AFFIDAVIT AND SWORN REPORT OF SYLVIA D. HALL-ELLIS, Ph.D.

Trial Date: June 18, 2018
Time: 9:30 a.m.
Department: 504

Exhibit 1018

Review of the Evidence Relating to Glyphosate and Carcinogenicity

Prepared for the Environmental Protection Authority
by Dr Wayne Temple BSc (Hons), PhD, FNZIC, CChem, FRSC, MAACT

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Introduction

Glyphosate (N-phosphonomethyl glycine; CAS registry #1071-83-6) is the primary active ingredient in many generic herbicides. Glyphosate is formulated primarily as an isopropylamine, ammonium, or sodium salt in water soluble concentrates and water soluble granules. The relevant impurities in glyphosate technical concentrates are formaldehyde, N-nitrosoglyphosate and N-nitroso-N-phosphonomethylglycine. Surfactants and sulfuric and phosphoric acids may be added to formulations of glyphosate, with type and concentration differing by formulation. The United States (US) Environmental Protection Agency (EPA) and other regulatory agencies around the world have registered this chemical as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate-based herbicides, which have been sold in the US since 1974, are now registered in over 130 countries.

Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential. The US EPA (1993) has classified glyphosate as a Group E carcinogen, which is defined as having "evidence of non-carcinogenicity for humans". This classification was based on "a lack of convincing evidence of carcinogenicity in adequate studies with two animal species, rat and mouse". Negative results were observed in genotoxicity studies that were conducted under good laboratory practice conditions and compliant with contemporary regulatory test guidelines.

However since that time, results of further studies have come to light, and the International Agency for Research on Cancer (IARC) Monograph 112 on glyphosate (released on 29 July 2015) came to the conclusion that glyphosate should now be classified as a carcinogenic substance in Group 2A (probably carcinogenic to humans). This classification was based on "limited evidence" from human data (regarding non-Hodgkin lymphoma (NHL)) but "sufficient evidence" in animal-experiments. The rationale identifies that the IARC working group (IWG) also notes mechanistic and other relevant data in support of the conclusion; in particular the IWG cites "strong evidence" that glyphosate can operate by two key characteristics of known human carcinogens, namely genotoxicity and oxidative stress.

This classification was initially published in a short report by Blair et al, (2015) in the "Lancet Oncology" on 20 March 2015.

This report discusses the relevant data on glyphosate, especially the more recent studies, and reviews the basis on which the IWG classified it as a probable human carcinogen (Group 2A). This involves review of the quality of evidence for carcinogenicity in humans and experimental animals and the mechanistic arguments.

Cancer in humans

The IWG found there was limited evidence in humans for the carcinogenicity of glyphosate. Some case-control studies of occupational exposure in the USA, Canada, and Sweden reported increased risks for NHL that persisted after adjustment for other pesticide exposures. However the Agricultural Health Study (AHS) cohort did not show a significantly increased risk of NHL. These studies are discussed below.

Case-control studies in the Midwest USA

Three case-control studies were conducted by the U.S National Cancer Institute in Iowa and Minnesota in the1980s using the same control series, but each investigating a different lymphohaematopoietic cancer. Brown et al, (1990) found a near null association between

glyphosate exposure and leukaemia among white males residing in the area (OR = 0.9; 95% CI 0.5–1.6). Among Iowa farmers reporting ever handling glyphosate, there was a slight non-statistically significant odds ratio for multiple myeloma (OR = 1.7; 95% CI 0.8–3.6) (Brown et al, 1993). Cantor et al, (1992) found an approximately null association between glyphosate exposure and NHL among males (OR 1.1; 95% CI 0.7–1.9).

The IWG reviewed a later study by De Roos et al, (2003) who used pooled data from three case-control studies of NHL conducted in the 1980s in Nebraska (Zahm et al, 1990), Iowa and Minnesota (Cantor et al, 1992), and Kansas (Hoar et al, 1986). Reported use of glyphosate as well as several other individual pesticides was associated with an increased risk of NHL. A total of 650 cases and 1,933 controls were included for the analysis of 47 pesticides. Reporting glyphosate exposure were 36 cases and 61 controls. After adjusting for other pesticide use, age, and study area, by two regression techniques, odds ratios of 2.1 (1.1–4.0) using logistic regression and 1.6 (0.9–2.8) using hierarchical regression were found.

In that regard, a later study by De Roos et al, (2005) where they reviewed the AHS cohort data is significant. They found no association between glyphosate and NHL. The authors noted that the aforementioned Midwest USA case control studies were retrospective in design and therefore potentially susceptible to recall bias as regards exposure reporting.

The cross-Canada case – control study

The IWG reviewed a report by McDuffie et al, (2001) who studied the association between NHL and exposure to specific pesticides in a multicentre population-based study with 517 cases and 1,506 controls among men of six Canadian provinces. The authors reported a slight, non-statistically significant increased risk for NHL from claimed glyphosate exposure, the OR being 1.26 (95% CI 0.87–1.80) for analysis adjusted for age and province, and 1.20 (95% CI 0.83–1.74) for analysis adjusted for age, province and high-risk exposures. The study also assessed the significance of different exposure durations. When stratified by greater than or less than two days of glyphosate exposure/year (< 2d/year), the values were 2.12 (95% CI 1.20–3.73) for >2d/year relative to those with < 2d/year (assigned OR of 1.0). The authors commented that although there was not a statistically significant finding for exposure to glyphosate per se, there was a dose-response relationship.

Case-control studies in Sweden

The IWG reviewed a study by Eriksson et al, (2008) who reported the results of a population-based case-control study of exposure to pesticides as a risk factor for NHL. Men and women aged 18–74 years living in Sweden were included from 1 December 1999 to 30 April 2002. In total, 910 (91%) cases and 1,016 (92%) controls participated. The authors found NHL associations with exposure to glyphosate. This exposure was reported by 29 cases and 18 controls, giving a reported odds ratio of 2.02 (95% CI 1.10–3.71) in a multivariate analysis. When restricted to a >10 year latency period the OR became 2.26 (95% CI 1.16–4.40). Odds ratios were also reported for lymphoma subtypes. For only two of the eight subtypes were odds ratios statistically significant; likely related to the small numbers. The IWG considered that this was a large study; that there was possible confounding from the use of other pesticides including MCPA, but this was controlled for in the analysis. Given the number of cases studied for glyphosate (29 cases and 18 controls) this study could hardly be considered as large. Twelve subjects were in a less than 10 days exposure group and 17 in a more than 10 days group. Therefore this study had limited power to detect an effect.

Other findings

In 2014 Schinasi and Leon reported their study of the association between NHL and occupational exposure to various agricultural pesticide chemical groups. Some findings on glyphosate were presented; for example the results from the studies by McDuffie et al, (2001), De Roos et al, (2005) and Eriksson et al, (2008) were given. This review included a series of meta-analyses, which they asserted showed consistent evidence of positive associations between NHL and carbamate insecticides, organophosphorus insecticides, lindane, and MCPA. As regards glyphosate (an "organophosphorus herbicide"), "in a handful of papers", associations between pesticides and NHL subtypes were reported; B cell lymphoma was positively associated with phenoxy herbicides and glyphosate.

The Agricultural Health Study (AHS) cohort studies

These studies in Ohio and North Carolina involve a large cohort of private and commercial pesticide applicators (57,311 as at 2004–5). Several studies have been conducted using this cohort.

Alavanja et al, (2003) evaluated associations between specific pesticides and prostate cancer in the AHS. Glyphosate was listed as one of the pesticides with sufficient exposure data for analysis, but the findings for it were not listed, so that it has been assumed that no significant positive association was found with prostate cancer.

Flower et al, (2004) evaluated associations between pesticide application by parents and cancer among children born to Iowa participants in the AHS. There was no positive association between either maternal or paternal use of glyphosate and risk of childhood cancer.

De Roos et al, (2005) evaluated associations between glyphosate exposure and "all cancers" or any cancer site using the AHS cohort. This study did not show a significantly increased risk of NHL. In the group reportedly exposed to glyphosate, small, non-statistically significant relative risks of 1.2 (95% CI 0.7–1.9) adjusted for age (only) and 1.1 (95% CI 0.7–1.9) adjusted for age, demographic and lifestyle factors and other pesticide exposure were found for NHL, (De Roos 2005). There was no dose (exposure) response relationship.

De Roos et al, (2005) also found a non-statistically significant association between glyphosate exposure and multiple myeloma, with rate ratios (RR values) of 1.1 (95% CI 0.5–2.4) adjusted for age only, and 2.6 (95% CI 0.7–9.4) adjusted for age, demographic and lifestyle factors and other pesticides exposures. Such a finding had not previously been reported.

Comparisons were made between ever-exposed versus never-exposed groups, and between three equal sized groups (tertiles), formed by subdivision either on the basis of total days of exposure or intensity-weighted exposure days. In the intensity-weighted analysis of glyphosate and lung cancer, the relative risk for the highest tertile was only 0.6 (95% CI 0.3–1.0), for pancreatic cancer the RR for the highest tertile was 0.5, while for multiple myeloma the RR was 2.1, but the confidence interval was wide (0.6–7.0). None of these findings reached statistical significance at 95%. Regarding the whole group (ie ever used glyphosate), the RR for multiple myeloma was 1.1 (95% CI 0.5–2.4) adjusted for age only, and 2.6 (95% CI 0.7–9.4) adjusted for age, demographic and lifestyle factors and other pesticide exposures. Unremarkable, non-statistically significant results were found for the other cancer sites assessed.

Thus as regards this study, there was no evidence of a statistically significant positive association for any of the cancers for which data were reported (Mink et al, 2012). Furthermore De Roos et al, (2005) acknowledged in their paper that over 13,000 subjects were excluded from multivariate analyses because of missing data. In analyses of "ever" versus "never" exposed to glyphosate, the age-adjusted relative risk of multiple myeloma was 1.1. Lash (2007) assessed the study design and concluded that adjustment for confounders, which resulted in limiting the data set by 25% because of missing data on the adjustment variables, likely introduced selection bias, which was likely to have been in the direction away from the null (ie exaggerating any possible risk).

It is also known that multiple myeloma is often preceded by monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant plasma cell disorder (Morgan et al, 2002). It is of interest to note that a decreased risk (albeit not statistically significant) of MGUS was observed in glyphosate applicators in the AHS.

Engel et al, (2005) evaluated breast cancer risk among wives of farmers in the AHS. No statistically significant association was found.

In an analysis of colorectal cancer and pesticide use, Lee et al, (2007) found no statistically significant association between glyphosate use and cancer of the colon or rectum.

Andreotti et al, (2009) reported no significant association of "ever" use (versus "never use") of glyphosate with pancreatic cancer among the combined group of AHS applicators and spouses (OR 1.1; 95% CI 0.6–1.07), nor was there evidence for a dose-response relationship.

Dennis et al, (2010) evaluated associations of 50 pesticides with cutaneous melanoma in the AHS cohort. Glyphosate was listed as one of the 22 pesticides on the enrolment questionnaire. The authors commented that none of these 22 pesticides was associated with melanoma.

None of the AHS cohort study analyses reported statistically significant positive findings for glyphosate exposure and total cancer or any site-specific cancer, in adults or children. In particular, the prospective AHS studies did not corroborate the positive association with NHL reported by the Swedish case-control studies. Analyses of increasing category of glyphosate exposure days and incidence of NHL produced rate ratios that were below the null value of 1.0 (De Roos et al, 2005 and Mink et al, 2012).

Discussion of review of epidemiological findings

In a review of glyphosate in 2006, the WHO observed that:
"widely used pesticides, like glyphosate, have recently become a focus of epidemiological research. In the past few years several epidemiological studies have been published that reported weak associations of glyphosate with lymphopoietic cancers, self-reported adverse reproductive outcomes and self-reported attention deficit hyperactivity disorder in children. However, the results of these studies do not meet generally accepted criteria from the epidemiology literature for determining causal relationships. Generally, the associations were rather weak and rarely statistically significant. Controlling for potential confounding factors, including other pesticides exposure, was not possible owing to limited available information and small numbers of subjects".

Whether or not there was any internal exposure or the extent of such exposure was not measured and, accordingly, a possible dose–response relationship could not be evaluated.

This seems a fair assessment of several of the studies regarding glyphosate and its formulations. De Roos et al, (2005) noted that the Midwest USA case control studies were retrospective in design and therefore potentially susceptible to recall bias as regards exposure reporting. Certainly a large prospective cohort study (such as that by De Roos et al, 2005) is much preferable to smaller case-control studies, the latter of which have much less statistical power to identify causal associations and are subject to more biases, including those regarding exposure assessment. Therefore much more weight should be given to the De Roos et al, (2005) cohort study than the much smaller De Roos et al, (2003) case-control study. In that regard, it is important to note that the cohort study found no association between glyphosate and NHL. There was, however, a small (non-statistically significant) increased risk of multiple myeloma in the 2005 study, but the point estimates of this risk may have been exaggerated. (Lash 2007.)

A re-analysis of some data from the De Roos et al, (2005) study has recently been undertaken, with a focus on multiple myeloma (Sorahan, 2015). Assessing the same data, Sorahan found no significant trends of multiple myeloma risk with reported cumulative days of glyphosate use, and unexceptional point estimates of risk for ever-use of glyphosate. This was irrespective of whether the analysis had made adjustment for a few basic variables (age and gender) or made adjustment for many other lifestyle factors or pesticide exposures; as long as data on all available pesticide applicators was used.

Sorahan (2015) argued that the elevated rate ratios (or relative risks) for multiple myeloma reported previously by Roos et al, (2005) arose from use of restricted data sets that, probably by chance, turned out to be unrepresentative. These restrictions were considered to be unnecessary and undesirable, as potentially informative data on the exposure or outcome under investigation were discarded. For example, it was asserted that there were a number of lost cases of multiple myeloma in the group of applicators who had never used glyphosate, because they were excluded by Roos et al, (2005) due to their not having data on for example use of alcohol, or smoking. These lost cases in the baseline category gave a false impression of elevated rates in ever-users. As a result Sorahan gave more weight to the point estimate of 1.1 as the RR (adjusted for age only) as opposed to the estimate of 2.6 as the RR for ever-use of glyphosate (adjusted for age, demographic and lifestyle factors, and other pesticides).

Mink et al, (2012) reviewed the epidemiological literature (and relevant methodological and biomonitoring studies) to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. Seven cohort studies and fourteen case-control studies examining a potential association between glyphosate and one or more cancer outcomes were subjected to a qualitative analysis.

The cohort studies were all based on analyses of participants or family members of the AHS cohort. Mink et al (2012), observed that none of the AHS cohort study analyses reported statistically significant positive findings for glyphosate exposure and total cancer or any site-specific cancer in adults or children. They found no consistent pattern of positive associations to suggest a causal relationship between human exposure to glyphosate and any cancer.

Overall, this 2012 review found no consistent pattern of positive associations between total cancer (in adults or children) or any site-specific cancer, and exposure to glyphosate. They suggested a cautious interpretation of the few positive associations reported, and concluded that the epidemiological data, when considered together, did not support a causal association between glyphosate exposure and cancer.

Similarly, the latest report of BfR (2015) to the European Food Safety Authority (EFSA)[1] based on the evaluation of over 30 epidemiological studies came to the overall assessment that there is no validated or significant relationship between exposure to glyphosate and an increased risk of NHL or other types of cancer.

A recent peer review by EFSA[2] (2015) essentially confirmed the conclusions in their re-evaluation of glyphosate. They noted that 10 cohort studies (which included the AHS, the largest series of prospective studies to date), found that glyphosate did not cause different types of cancer and did not increase risk of all cancers combined. (As noted earlier, the findings for NHL were negative in the AHS cohort.) Similarly nine case-control studies did not indicate an increased risk of carcinogenicity, or did not have sufficient power to assess this. With regard to NHL, the case-control studies exhibited poor consistency in their results and small numbers of cases limiting the statistical significance of findings in some studies. As noted above, case-control studies have less power, are more subject to various biases, and are less effective at assessing actual exposure levels than are cohort studies. EFSA concluded that there is very limited evidence for an association between glyphosate exposure and the occurrence of NHL.

Cancer in experimental animals

Mice studies

Glyphosate was tested in female and male mice by dietary administration in two studies. A skin application in one initiation-promotion study was conducted with male mice.

The IWG found that in male CD-1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma. A second study reported a positive trend for hemangiosarcoma in male mice. A glyphosate formulation promoted skin tumours in an initiation-promotion study in mice.

The IWG noted there was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in male CD-1 mice in a glyphosate feeding study (0, 1,000, 5,000, or 30,000 ppm glyphosate *ad libitum* for 24 months). (This study was conducted prior to the institution of GLP.) The study was submitted to the US EPA which requested that a pathology working group (PWG) be convened to evaluate the renal tumours. In this second evaluation, the PWG found that the incidence of adenoma was not statistically significant but the incidence of carcinoma and the incidence of adenoma and carcinoma (combined) were significant. The IWG considered that this second evaluation indicated a significant increase in the incidence of rare tumours, with a dose-related trend, which could be attributed to glyphosate.

However, this finding is at variance with the US EPA (1993) which reported in their glyphosate review that the occurrence of these adenomas was spontaneous rather than compound-induced because the incidence of renal tubular adenomas in males was not statistically significantly different when compared with the concurrent controls. An independent group of pathologists and biometricians also conducted extensive evaluations of these adenomas and reached the same conclusion. The US EPA concluded glyphosate was not considered to be carcinogenic in this study.

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[1] The BfR (2015) report addressing the carcinogenicity of glyphosate is a report of Germany specifically, as Germany was the lead member state for the EFSA review of glyphosate.

[2] EFSA accepted the conclusion relating to glyphosate and cancer (including NHL), with one dissenting member state.

The IWG reviewed a second feeding study reported to the FAO/WHO Joint Meeting on Pesticide Residues (JMPR), and found there was a significant positive trend in the incidence of hemangiosarcoma in male CD-1 mice. Groups of 50 female and male mice were fed diets containing glyphosate at a concentration that was adjusted weekly for the first 13 weeks and every four weeks thereafter to give doses of 0, 100, 300, or 1,000 mg/kg body weight, *ad libitum* for 104 weeks.

In contrast JMPR (WHO 2006) found that owing to the lack of a dose-response relationship, the lack of statistical significance and the fact that the incidences recorded in this study fell within the historical ranges for controls, these changes were not considered to be caused by administration of glyphosate. They concluded administration of glyphosate to CD-1 mice for 104 weeks produced no signs of carcinogenic potential at any dose.

Initiation-promotion

The IWG found that in a study involving 20 male Swiss mice which had a glyphosate based formulation applied to their skin, it appeared to be a tumour promoter, but they concluded that this was an inadequate study because its design was poor, with short duration of treatment, no solvent controls, small numbers of animals, and a lack of histopathological examination.

However the BfR (2015) considered that generally testing of formulations should not be used for the toxicological evaluation of active substances because co-formulants may extensively alter the outcome. The BfR deemed that this IWG finding was not considered by the institutions in the EU to be evidence for the carcinogenic properties of glyphosate per se.

Review articles – mice studies

The IWG noted that Griem et al, (2015) had published a review article which included discussion of five long-term glyphosate feeding studies in mice. Two of the studies were discussed in the IARC monograph. The working group summarised the other three studies but claimed that it was unable to fully evaluate the other three studies because of the limited experimental data provided in the review article and supplemental information.

Griem et al, (2015) noted that the five mouse studies that they reviewed were submitted to support glyphosate renewal in the EU. They considered that all but the oldest study were reliable without restriction and were performed under conditions of GLP and OECD protocols.

During the EFSA peer-review process for the renewal of the approval of glyphosate, EFSA also received a complementary mandate from the EU to consider the findings by IARC regarding the potential carcinogenicity of glyphosate (EFSA 2015).

The EFSA peer review (2015) also evaluated the five mice studies. Only one of these suggested a potential carcinogenic effect, as evidenced by a statistically significant increased evidence of malignant lymphomas at the top dose level of 1,460 mg/kg/day. However the validity of the study was questioned, due to the occurrence of viral infection which could have influenced survival rates and the incidence of lymphomas. No carcinogenic effects were observed at the highest dose levels in any of the other studies. The IWG evaluated two of these studies and asserted positive trends in males for renal tubular carcinomas in one study and for hemangiosarcoma in the other. However EFSA took a weight-of-evidence approach; with considerations including the statistical significance being only found in trend analysis but not in pairwise comparison, lack of consistency in multiple

animal studies, the fact that the slightly increased incidences only occurred at doses higher than those recommended for the oral route in carcinogenicity studies, incidences in test animals generally being within the historical range for control groups, and the lack of pre-neoplastic lesions.

Rat studies

Five feeding studies in rats and two drinking water studies with glyphosate were reviewed by the IWG.

Drinking water

One study in Sprague-Dawley rats was considered by the IWG to be inadequate for evaluation because of its short exposure duration.

A glyphosate containing drinking water study with Wistar rats did not show any significant increase in tumour incidence.

Dietary administration

Two studies in Sprague-Dawley rats showed a significant increase in the incidence of pancreatic islet cell adenoma in male rats. One of these studies also showed a significant positive trend in the incidence of hepatocellular adenoma in males and of the thyroid C-cell adenoma in females. However two studies (one in Sprague-Dawley and one in Wistar rats) found no significant increase in tumour incidence at any site.

The IWG reviewed a chronic feeding study (provided by the US EPA) in which groups of 60 female and male Sprague Dawley rats were given diets containing glyphosate at a concentration of 0, 2,000, 8,000 or 20,000 ppm *ad libitum* for 24 months. In males at the lowest dose, there was a statistically significant increase in the incidence of pancreatic islet cell adenoma compared with controls. Additional analyses by the US EPA revealed a statistically significant higher incidence of pancreatic islet cell carcinoma in males at the lowest and highest doses compared with controls: lowest dose, 8/45 (18%); intermediate dose, 5/49 (10%); highest dose, 7/48 (15%) versus controls, 1/43 (2%). The range for historical controls for pancreatic cancer islet cell carcinoma reported in males at this laboratory was 1.8–8.5%. The IWG concluded that this study demonstrated a significant increase in the incidence of pancreatic islet cell adenoma in male rats.

However the US EPA (1993) had concluded that:
"these adenomas were not treatment-related and glyphosate was not considered to be carcinogenic in this study. With respect to pancreatic islet cells adenomas, there was no statistically significant positive dose-related trend in their occurrence; there was no progression to carcinomas; and the incidence of pancreatic hyperplasia (non-neoplastic lesion) was not dose-related. With respect to hepatocellular adenomas, the increased incidence of these neoplasms was not statistically significant in comparison with the controls; the incidence was within the historical control range; there was no progression to carcinomas; and the incidence of hyperplasia was not compound-related. With respect to thyroid C-cell adenomas, there was no statistically significant dose-related trend in their occurrence; the increased incidence was not statistically significant; there was no progression to carcinomas; and there was no significant dose-related increase in severity or incidence of hyperplasia in either sex".

Also, in the JMPR (WHO 2006) review of this study they reported:
"The historical-control range for this tumour at the testing laboratory was 1.8–8.5%, but a partial review of studies reported recently in the literature revealed a prevalence of 0–17% in control males with several values being ≥ 8%. More importantly, the incidences of islet cell adenomas clearly did not follow a dose-related trend in the treated groups of males. There was no evidence of dose-related pancreatic damage or pre-neoplastic lesions. The only pancreatic islet cell carcinoma found in this study occurred in a male in the control group, thus indicating a lack of treatment-induced neoplastic progression. Taken together, the data support the conclusion that the occurrence of pancreatic islet cell adenomas in male rats was spontaneous in origin and unrelated to administration of glyphosate".

Review articles – rat studies

The IWG noted that Griem et al, (2015) had published a review article containing assessments of nine long-term glyphosate feeding studies in rats. Five of these studies were reviewed by the IWG. The remaining four studies were not evaluated by the IWG which stated that there was limited experimental data provided in the review article. These four studies had been submitted to various organisations for registration purposes. There was no evidence of a carcinogenic effect related to glyphosate treatment.

Its long-term toxicity and carcinogenicity was assessed in nine rat studies. The EFSA peer review concluded that no significant increase in tumour incidence was apparent. Three of these studies were not evaluated by the IARC panel. In two studies, increased incidences of pancreatic islet cell adenomas were found but were not dose-related. EFSA also noted that the significance of these findings depended on the statistical analysis: using a pairwise comparison (as planned for in the study protocol) no significant effect is observed, whereas a trend analysis performed by the IWG identified significant changes. EFSA noted that deviations from the statistical analysis used by the study authors should be limited and properly justified.

Other relevant data

The IWG group noted that soil microbes degrade glyphosate to aminomethylphosphonic acid (AMPA). Blood AMPA detection after glyphosate poisoning incidents suggests intestinal microbial metabolism in humans.

Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Neimann et al, (2015) published a critical review and comparison of data obtained in a total of seven studies from Europe and the US. They concluded that no health concern was revealed because the resulting exposure estimates were several magnitudes lower than the acceptable daily intake (ADI) or the acceptable operator exposure level (AOEL).

The measured internal exposure was clearly below the worst-case predictions made in the evaluation of glyphosate as performed for the renewal of its approval within the European Union.

This is consistent with the risk-based approach that regulatory agencies use when considering realistic dosages and real-life conditions. Those studies show that farmers and farm families are exposed to significantly lower doses of the herbicide than some model estimates would suggest.

It is also in keeping with an earlier review (Williams et al, 2000) of the animal data, in which dose levels from animal toxicity tests were compared to conservative, upper-limit estimates

of human exposure to glyphosate, to give a margin of exposure (MOE) value. MOE analyses compare the lowest NOAELs determined from animal studies to worst-case levels of human exposure; with MOEs of greater than 100 indicating confidence that no adverse health effects would occur. These authors found in their review that the MOEs for worst-case chronic exposure to glyphosate ranged from 3,370 to 5,420, and concluded that "under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans".

Genotoxicity

The IWG claimed that there is strong evidence that glyphosate is genotoxic. They tabulated numerous reports of tests relating to the genotoxicity of glyphosate and its formulations, with some showing a positive association, and some a negative association.

The evaluation of the large volume of genotoxicity data available requires consideration of assay system validation, test system species used, relevance of the endpoint to heritable mutation, reproducibility and consistency of effects and dose-response, and relationship of effects to toxicity. The guidelines for genetic toxicology tests developed for the OECD are a pre-eminent source of internationally agreed guidelines.

There were often inconsistent results reported (both positive and negative) from the same test systems in different laboratories. The relevance of many of the assays in test system species (fish, oysters, insects, snails, worms and caimans) which have never been validated for the assessment of genotoxicity in humans for regulatory purposes, is questionable. Additionally the *intraperitoneal* route of exposure for many of the mammalian *in vivo* studies is not appropriate since it does not reflect normal human exposure, with doses exceeding occupational exposure by orders of magnitude.

Kier and Kirkland (2013) published a review of the genotoxicity of glyphosate and glyphosate-based formulations. This review concluded that there was a strong weight of evidence that glyphosate and its formulations are predominantly negative in well-conducted, core bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays. Although some positive results for glyphosate and glyphosate-based formulations were reported in DNA damage assays, and for the micronucleus endpoint for formulations in non-mammalian studies, the positive results were associated with high dose levels and/or overt toxic effects. The preponderance of negative results in core assays supports the conclusion that reports of DNA damage or non-mammalian micronucleus effects are likely to be secondary to cytotoxicity rather than indicative of DNA-reactive mechanisms.

The IWG found that glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells *in vitro*. They referred to one study (Bolognesi, 2009) reporting increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations, to support this contention of genotoxicity.

However, the authors of the Bolognesi (2009) study concluded that overall, data suggesting that genotoxic damage (as evidenced by the micronuclei test) associated with glyphosate spraying for control of illicit crops is slim, and any such effect appears to be transient. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for coca and poppy eradication is low. The attribution of a genotoxic effect due to glyphosate exposure rather than a multitude of other demographic and environmental causes seems rather tenuous given the uncertainty of actual exposure.

In a recent communication, EFSA summarised their appraisal of the genotoxicity studies. *In vitro* tests of mutagenicity gave consistently negative results. *In vitro* tests of mammalian chromosome aberration (all of those which had been performed under GLP conditions) were also negative. Positive results were found in some published *in vitro* studies of chromosomal aberrations, but these were not confirmed by *in vivo* studies addressing the appropriate endpoints, such as the micronucleus test.

As regards *in vivo* tests, all studies conducted according to internationally validated guidelines for good laboratory practice (GLP) and some non-GLP published studies gave negative results. Two non-GLP studies were positive in mice treated intraperitoneally, but at levels close to or above the LD_{50}[3] (possibly suggestive that this is a secondary effect), and one study had major flaws. No genotoxic effects on germ cells have been detected in rats or mice treated orally at dose levels up to 2,000 mg/kg/day (the maximum dose level recommended for such studies). EFSA concluded that, considering the weight of evidence, glyphosate is unlikely to be genotoxic *in vivo*.

As regards glyphosate-based commercial formulations, a number of formulations with unknown composition have given positive results when tested *in vitro* and *in vivo*. However some of the test systems are not validated and/or interpretation is difficult due to possible confounding, such as cytotoxicity, specific organ toxicity or unclear relevance to humans (such as tests in fish, amphibians, or invertebrates). Some of the co-formulants (such as polyethoxylated tallow amine (often abbreviated to POEA)) may be more systemically toxic than glyphosate. However EFSA concluded that the genotoxic potential of such complete formulations should be further assessed.

Kier (2015) reviewed genotoxicity biomonitoring studies of glyphosate-based formulations. He found that most of the human biomonitoring studies were not informative because there was either a very low frequency of exposure to glyphosate formulations or exposure to a large number of pesticides in addition to glyphosate without analysis of specific pesticide effects. One pesticide sprayer biomonitoring study indicated there was no statistically significant relationship between frequency of exposure to glyphosate formulations reported for the last spraying season and oxidative DNA damage. There were three studies of human populations in regions of glyphosate formulation aerial spraying. One study found increases for the cytokinesis-block micronucleus endpoint but these increases did not show statistically significant associations with self-reported spray exposure and were not consistent with application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study two years after spraying did not indicate chromosomal effects.

Oxidative stress

The IWG found that glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and *in vitro*.

Oxidative stress was only found in one study in rats administered intraperitoneal glyphosate active ingredient (Astiz et al, 2009), and in numerous studies using *intraperitoneal* administration or *in vitro* methods with glyphosate-based formulations. However, these studies used doses that exceeded normal occupational exposures by orders of magnitude and the *intraperitoneal* route of exposure is not appropriate for evaluating human exposure. Glyphosate has low gastrointestinal absorption and poor dermal absorption. It therefore

[3] LD_{50} is the dose of the substance required (usually expressed in relation to body weight) that is estimated to kill 50% of the test population.

seems unlikely that human exposure would produce the sort of tissue levels used in the oxidative stress tests. There was also some inconsistency in results.

Most effects were seen when whole glyphosate formulations were tested. EFSA considered that generally testing of formulations should not be used for the toxicological evaluation of active substances because co-formulants may extensively alter the outcome. Thus any effects found cannot then be attributed to the glyphosate active ingredient present.

Discussion

The IARC WG (IWG) classified glyphosate as "probably carcinogenic to humans (Group 2A)" as the overall evaluation.
As set out in their evaluation section, this was based on:

- "*limited evidence*" in humans for the carcinogenicity of glyphosate, and
- "*sufficient evidence*" in experimental animals for carcinogenicity of glyphosate.

The rationale identifies that the IWG also notes mechanistic and other relevant data in support of the conclusion; in particular the IWG cites "strong evidence" that glyphosate can operate by two key characteristics of known human carcinogens, namely genotoxicity and oxidative stress.

This discussion section of the report will consider each of these sources of evidence in turn as contributing factors to the IWG's overall evaluation.

Human epidemiological evidence

The key cited studies in support of the "limited evidence" in humans for carcinogenicity of glyphosate consisted of three case-control investigations. The odds ratios (OR) for cases of NHL and glyphosate exposures are summarised in the following table.

Odds ratios (OR) for cases of NHL and glyphosate exposures

Study area	OR[1] and 95% CI[2]	Study reference
Midwest, USA	2.1 (1.1–4.0) [logistic regression] 1.6 (0.9–2.8) [hierarchical regression]	De Roos et al, 2003
Canada	1.26 (0.87–1.8) 1.20 (0.83–1.74) [adjusted for medical variables]	McDuffie et al, 2001
Sweden	2.02 (1.1–3.71) [univariate] 1.51 (0.77–2.94) [multivariate]	Erikson et al, 2008

1. OR is the odds ratio of outcome of interest between the relevant case group and the reference or control group.
2. The 95% CI are the confidence intervals round the OR representing the limits within which there is 95% confidence that the true value falls.

The first important observation is that depending on the statistical tests used only two studies (Midwest USA and Sweden) show OR values indicating statistical significance at the 95% level. In the Midwest USA, however, this is only true using logistic regression, while in the Swedish study only the univariate analysis showed statistical significance.

Some case control studies assessed data using dose (exposure)/response or intensity/response to determine whether or not there is a trend to a higher incidence of tumours in persons categorised as having higher exposures to glyphosate. While these approaches are desirable, the criteria of exposure seem low. For one case-control study, the criterion for high or lower glyphosate use was greater than or less than two days of glyphosate use/year (McDuffie et al, 2001), whereas in another the criterion was greater than or less than 10 days of glyphosate use/year (Eriksson et al, 2008). While the distribution of use category was not given in either study, 2–10 days of use per year seems a low benchmark for exposure comparisons. The direct glyphosate exposure findings with respect to NHL was not significant in the McDuffie et al, 2001 study, but they reported a dose response based on this dose comparison and quoted the OR for exposure >2 day/year as 2.12 (95% CI 1.20–3.73).

The direct glyphosate exposure findings with respect to NHL were significant in the Swedish study using univariate evaluation, and the effect of dose-response in the Swedish study appears to only be statistically significant using this approach (considering the data presented in the IARC Monograph in Table 2.2, p23) which reported a higher OR for "heavy" users (>10 days/year) of 2.36 (95% CI 1.04–5.37). It is noteworthy that the paper reports the highest OR, 2.81 (95% CI 1.27–6.22), for the association between exposure to MCPA and NHL. This may be the explanation for the difference between the results using univariate and multivariate evaluation. When considering the latency period, >10 years exposure to glyphosate had an OR of 2.26 (95% CI 1.16–4.4) in comparison to ≤ 10 years with an OR of 1.11 (95% CI 0.24–5.08), but these findings may be confounded by exposure to MCPA or other phenoxy herbicide exposures. There could be residual confounding from MCPA exposure if the participants under-reported earlier MCPA exposure. The apparent increased risk with latency for glyphosate exposure could be because participants who had sprayed pesticides for longer were more likely to have used the phenoxy herbicides (including MCPA) earlier in their working lives.

The AHS cohort study (De Roos, et al, 2005) had a more detailed assessment at different exposure intensities as they used cumulative lifetime days of use and an intensity measure (years of use x days/year x estimated exposure level). The data (presented in Table 2.1 of the IARC Monograph on p12) for this cohort study showed no statistically significant difference for the trend to increased exposure with exposure bands at 0–20, 21–56 and 57–2,678 cumulative days of exposure, despite the higher exposure levels in comparison to the case-control studies.

It is important in these circumstances to consider the overall data set. Rather than only highlighting the three case-control studies which identified a marginally statistically significant association between reported glyphosate use and NHL, the overall assessment needs to take into account other studies which did not demonstrate such an association. Also, it is particularly important to note the lack of significant finding in a large cohort study (the AHS) where the potential for recall bias is greatly reduced and should therefore be given greater weight than the case control studies. Cohort studies are generally considered more reliable than case-control studies, because the population is defined and the exposure parameters and the potential confounding exposures and lifestyle factors are established prior to the adverse outcome of interest so that the potential for recall bias is less likely.

Given the lack of confirmation of the small number of positive findings from case-control studies in the more powerful cohort study, the epidemiological support for the conclusion "limited evidence" in humans is not convincing.

Experimental animal studies
The key cited studies in support of the "sufficient evidence" in experimental animals for carcinogenicity of glyphosate consisted of three studies in mice. These comprised one oral study demonstrating a positive trend for increased incidence of renal tubule carcinoma, one oral study in mice demonstrating a positive trend for increased incidence of hemangiosarcoma; and a supporting skin study demonstrating tumour promotion using a glyphosate formulation. In addition, one rat study demonstrated an increased incidence of pancreatic islet cell adenomas.

In assessing these data, the IWG used different statistical tests to those in the original analysis (trend analysis rather than a pairwise comparison against controls). The original studies were designed with the intention to assess statistical significance by means of a pairwise comparison between the test and control groups, so use of the trend assessment by IARC to assess these data requires justification. IARC's use of the trend assessment gave a positive response, but in none of the studies are the positive effects statistically significant using the original statistical approaches. Also, the IWG did not take into account the generally accepted assessment of the same data by international panels of experts, which took into account additional historical incidence data for hepatocellular adenomas in the rats and the presence of a viral infection in the mouse study which could have influence survival rates and the incidence of lymphomas.

The promotion study using a glyphosate-based formulation should not be used as support for the carcinogenicity of glyphosate per se, since the test substance contains other components which might influence the outcome.

The IWG did not evaluate some other studies which have been used by other regulators. These did not support the view that exposure to glyphosate in long-term feeding studies was associated with an increase in tumours at any sites. While the IWG approach is consistent with the IARC pre-amble and policy on the selection of study data, in the current circumstances this attributes inappropriate weight to the three studies which IWG considered and for which their analysis found an increase in tumours. Firstly because other studies which other reputable bodies found to be negative were not considered, and secondly because the reasons why the above findings were not relied upon by other assessments were not taken into account by the IWG. In particular a lack of consistency (dose-response) in multiple studies, slight increases in incidence at the maximum tested dose only, or incidences within the historical control range.

Taking into account that the positive findings cited by the IWG were not assessed as evidence of a carcinogenic effect in the view of other reputable bodies, and that the total data set of long-term carcinogenicity bioassays were consistently negative, it is concluded that the overall weight of evidence does not indicate that glyphosate is carcinogenic.

Mechanism of action
The IWG cites what is described as "strong evidence" that glyphosate can operate by two key characteristics of known human carcinogens – genotoxicity and oxidative stress. The studies used in support of this conclusion were primarily *in vitro* mammalian cell studies. In such studies the mammalian cells are directly exposed to the test substance (glyphosate or a glyphosate-based formulation) at high concentrations which would not be reasonably achieved in an *in vivo* exposure whether in animals or humans. All studies done according to internationally validated guidelines gave negative results, while studies using unvalidated

test method/species, or with glyphosate-containing formulations or using high *intraperitoneal* doses are inappropriate for assessment of genotoxicity to humans.

Other supporting evidence for this conclusion included DNA damage and micronuclei in various populations allegedly exposed to glyphosate from sprays. Attributing the effects found to the exposure to glyphosate is questionable when the exposure, if any, was to glyphosate-based formulations and unidentified demographic, geographical or lifestyle factors that could be responsible for the DNA damage.

In relation to oxidative stress this was only found in one study in rats administered *intraperitoneal* glyphosate active ingredient (Astiz et al, 2009), and in numerous studies using *intraperitoneal* administration or *in vitro* methods with glyphosate-based formulations. The *intraperitoneal* route of administration is not considered relevant to human exposures. Glyphosate has low gastrointestinal absorption and poor dermal absorption. There was also some inconsistency in results. So the evidence for glyphosate causing oxidative stress is considered weak.

Conclusion

The overall conclusion is that – based on a weight of evidence approach, taking into account the quality and reliability of the available data – glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification under HSNO as a carcinogen or mutagen.

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Exhibit 1019

Regulatory position: consideration of the evidence for a formal reconsideration of glyphosate

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CONTENTS

TABLES

FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994.*

The APVMA has legislated powers to reconsider the approval of an active constituent, registration of a chemical product or approval of a label at any time after it has been registered. The reconsideration process is outlined in sections 29 to 34 of Part 2, Division 4 of the Agvet Codes.

A reconsideration may be initiated when new research or evidence raises concerns about the use or safety of a particular chemical, a product containing that chemical, or its label. The scope of each reconsideration can cover a range of areas including human health (toxicology, public health, occupational health and safety), the environment (environmental fate and ecotoxicology), residues and trade, chemistry, efficacy or target crop/animal safety. However, the scope of each reconsideration is determined on a case-by-case reflecting the specific issues raised by the new research or evidence.

The reconsideration process (illustrated in Figure 1) includes a call for information from a variety of sources, a review of that information and, following public consultation, a decision about the future use of the chemical or product. The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be generated according to scientific principles. The APVMA conducts science and evidence-based risk analysis with respect to the matters of concern, analysing all the relevant information and data available.

When the APVMA receives or is made aware of a significant new piece of information that questions the safety (to target animals, humans or the environment) or efficacy of a registered chemical, the APVMA assesses the new information to determine whether a formal reconsideration of that chemical and/or products containing that chemical should be initiated.

In undertaking this process, the APVMA works in close cooperation with external experts including the Department of Health, Food Standards Australia New Zealand (FSANZ), the Department of the Environment and Energy and the state departments of agriculture, as well as other expert advisers as appropriate.

This document sets out the nomination assessment process for glyphosate that was initiated following the classification of glyphosate as 'probably carcinogenic to humans' by the International Agency for Research on Cancer (IARC) in March 2015.

This document and the technical reports relating to glyphosate are available from the APVMA website at www.apvma.gov.au. The technical reports are:

- Review of IARC Monograph 112 (Glyphosate): Tier 1
- Review of IARC Monograph 112 (Glyphosate): Tier 2.

1. Nomination	**Nomination.** Any person or group (including the APVMA and its partner agencies) may nominate an active constituent, product or label for reconsideration. The APVMA assesses the supporting scientific information and determines whether a reconsideration is warranted. Not all nominations will proceed to a formal reconsideration—there are other regulatory pathways available that may more efficiently address concerns. **The APVMA nominated glyphosate for reconsideration following the classification of glyphosate as 'probably carcinogenic to humans' by the International Agency for Research on Cancer in 2015**.	
2. Prioritisation	**Prioritisation.** The APVMA (with input from its advisory agencies) determines the priority of the reconsideration.	
3. Scoping and work plan	**Scope.** A scope document is prepared that outlines the areas of concern to be reconsidered. From 1 July 2015 the APVMA is legislatively required to publish a **work plan** for all reconsiderations to provide predictability about the timeframe for the reconsideration.	
4. Notice of reconsideration	**Notice of reconsideration.** To begin the reconsideration, the APVMA gives each holder a written Notice of Reconsideration that invites the holder to make a written submission to the APVMA. The holder is legally obliged to submit any available data relevant to the scope of the reconsideration. The APVMA supplements the submitted data with data available in the public domain (eg peer-reviewed scientific journal articles or international assessment reports).	
5. Assessment	**Toxicology assessment.** The toxicology assessment characterises all of the adverse health effects that a compound may cause and establishes health-based guidance values (also known as public health standards) for exposure to the chemical. The toxicology assessment recommends first aid directions, poisons scheduling and any necessary warnings for product labels.	**Environment risk assessment.** Where indicated in the scope of the reconsideration, an environmental risk assessment is conducted. The environmental risk assessment may include an evaluation of environmental fate and ecotoxicology.
	Human exposure assessment. The Toxicology assessment findings are used in the Occupational Health and Safety (human exposure) assessment. This assessment recommends safety directions, re-entry periods and restraints for all the uses supported by the assessment.	**Residues and dietary exposure risk assessment (includes trade).** The available residues data are used in the residues and dietary exposure risk assessment. This assessment recommends withholding periods, MRLs and restraints for all use patterns supported by this assessment. It also considers the potential trade risks arising from all the supported uses of products.
	Efficacy: If included in the scope of the review efficacy assessments are conducted by the APVMA.	

6. Draft regulatory measure	**Interim Regulatory Action.** At any time during a reconsideration, the APVMA may take regulatory action to mitigate any risks identified in relation to the use of a chemical. The aim of any such action is to protect human health or the environment (or both) while a final decision is being reached through the reconsideration process. **Proposed Regulatory Decision.** The APVMA considers all the assessments and develops draft recommendations for the reconsideration which summarise the results of the assessment, identified risks, risk mitigation measures, proposed review findings and draft regulatory decisions. The PRD and the component assessment reports are released for public consultation.
7. Consultation	**Consultation.** Further data or information may be submitted to the APVMA from a range of stakeholders including holders, users of the chemicals, peak industry bodies, interest groups, non-government organisations, state and territory governments or the public. Usually a 3-month public consultation period is conducted following publication of the PRD. Any further data or information submitted during consultation will be taken into consideration before making the final regulatory decision.
8. Regulatory decision	**Regulatory decision**. After the public consultation period has closed, the APVMA assesses all the comments received and amends the assessment, review findings and the proposed regulatory measures as necessary. We then make the final regulatory decision. There are three possible regulatory outcomes from a reconsideration: • affirm the approvals or registrations • vary the relevant particulars or conditions and affirm the approval or registration, or • suspend or cancel the approval or registration. The APVMA will affirm the approval or registration only if satisfied that it meets all statutory safety, efficacy, trade and labelling criteria and also complies with all requirements in the regulations If the active constituent, product or label does not meet the criteria as described above, the APVMA will examine whether the relevant particulars or conditions of the approval or registration can be varied so that the criteria can be met. This may include varying the instructions for use on the label. If product registrations or label approvals are cancelled the APVMA will examine whether a phase out period for dealing with or using cancelled products or products bearing cancelled labels is appropriate. Additional instructions may be applied during phase out. If a phase out period is not appropriate then recall action may be required.
END OF RECONSIDERATION (regulatory decision)	
9. Implementation	**Implementation.** Once the decision is made to affirm, cancel or vary conditions of registrations or approvals the APVMA will send written Notices to the holders of registrations and approvals and publish Notices of affirmation, variation of conditions, and cancellation of actives, products or label approvals. These Notices will include brief statements of the reasons for the actions, relevant particulars for any affirmed approvals or registrations and any appropriate instructions of use or phase-out periods for cancellations. The APVMA will publish details of any applicable phase out periods if any approvals of actives, registration of products or label approvals are cancelled. The maximum legislated phase out period is 12-months.

Figure 1: The chemical reconsideration process

SUBMISSIONS FROM THE PUBLIC ARE INVITED

This draft regulatory position report:

- outlines the APVMA chemical reconsideration process
- advises interested parties how to respond to the assessment
- summarises the nomination assessment methodology and outcomes
- outlines the proposed regulatory position to be taken in relation to the nomination for reconsideration of glyphosate and products containing glyphosate.

The APVMA invites persons and organisations to submit their comments and suggestions on this nomination assessment report directly to the APVMA. Comments on this report will be assessed by the APVMA before the report is finalised and the final regulatory position report is published.

Submissions can be sent to:

Director, Chemical Review
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182

KINGSTON ACT 2604

Telephone: +61 2 6210 4749
Facsimile: +61 2 6210 4776
Email: chemicalreview@apvma.gov.au
Website: www.apvma.gov.au.

Preparing your comments for submission

Please limit any comments you have to the scientific justification for the proposed regulatory position on glyphosate.

When making your comments:

- clearly identify the issue and clearly state your point of view
- give reasons for your comments, supporting them with relevant scientific information and indicating the source of the information you have used.

Please try to structure your comments in point form, referring each point to the relevant section in the regulatory position report. This will help the APVMA assemble and analyse all of the comments it receives.

When making a submission, please include:

- contact name

- company name or group name
- postal address
- email address (if available)
- the date you made the submission.

Finally, tell us whether the APVMA can quote your comments in part or full.

Please note that, subject to the *Freedom of Information Act 1982*, the *Privacy Act 1988* and the Agvet Code, all submissions received may be made publicly available. They may be listed or referred to in any papers or reports prepared on this subject matter.

The APVMA reserves the right to reveal the identity of a respondent unless a request for anonymity accompanies the submission. If no request for anonymity is made, the respondent will be taken to have consented to the disclosure of their identity for the purposes of Information Privacy Principle 11 of the *Privacy Act 1988*.

The contents of any submission will not be treated as confidential or confidential commercial information unless they are marked as such and the respondent has provided justification for the material to be classified as confidential or confidential commercial information in accordance with the *Freedom of Information Act 1982* or the Agvet Code, as the case may be.

THE CLOSING DATE FOR SUBMISSIONS IS FRIDAY 30 DECEMBER 2016.

EXECUTIVE SUMMARY

Introduction

Glyphosate is a broad-spectrum, non-selective, post-emergent, systemic herbicide that kills or suppresses all plant types (except those genetically modified to be resistant to glyphosate) and is commonly used to control annual and perennial broadleaf and grassy weeds in various agricultural and non-agricultural settings. Glyphosate acts by disrupting the shikimic acid pathway, which is unique to plants, to prevent protein biosynthesis and kill the plant.

The first product containing glyphosate was registered for use in Australia in the 1970s, under the trade name 'Roundup®'. Products containing glyphosate that are registered for use in Australia are formulated as solutions, granules, aerosols and gels and are generally applied using ground or aerial equipment.

Concerns have recently been raised about human exposure to glyphosate, following an assessment by the International Agency for Research on Cancer (IARC) that re-classified glyphosate as 'probably carcinogenic to humans'.

The APVMA chose to consider glyphosate for reconsideration following the publication of the IARC Monograph 112 in July 2015. Once a chemical has been nominated for reconsideration, the APVMA examines the new information to determine whether there are sufficient scientific grounds to warrant placing the chemical under formal reconsideration. This regulatory position report represents the outcome of that scientific nomination assessment process.

Evaluation methodology: a weight-of-evidence approach

The nomination assessment process involved a scientific weight-of-evidence evaluation of information in the IARC monograph, risk assessments undertaken independently by regulatory agencies in other countries and expert international bodies, in addition to Adverse Experience Reports (AERs) submitted to the APVMA. A weight-of-evidence assessment involves an examination of the quality, biological relevance and consistency of studies, assessment reports and scientific conclusions according to the scientific method.

The APVMA commissioned a review of the IARC monograph by the Office of Chemical Safety (OCS) within the Department of Health. This review was conducted in two phases: Tier 1 involved conducting a preliminary scoping review of the IARC monograph to ascertain the relevance of the carcinogenicity classification of glyphosate and any implications that this may have for glyphosate approvals and registrations in Australia; Tier 2 involved conducting a detailed assessment of those studies that were identified during the Tier 1 assessment as requiring further evaluation.

The APVMA also reviewed a number of very recent international assessments of glyphosate including those undertaken by the Joint Food and Agriculture Organisation of the United Nations/World Health Organisation (FAO/WHO) Meeting on Pesticide Residues, the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), Health Canada and the New Zealand Environmental Protection Authority (NZ EPA).

Assessment of the IARC glyphosate monograph

The OCS undertook a screening level assessment of the IARC monograph (Tier 1) and identified 19 references relevant to the carcinogenicity classification of glyphosate requiring a more in-depth evaluation, with an additional 74 references requiring further review to determine their relevance—the APVMA utilised recent independent international assessments of these references. Following the assessment of the 19 studies relevant to the IARC carcinogenicity classification of glyphosate (Tier 2), the OCS concluded that there did not appear to be any new information to indicate that glyphosate poses a carcinogenic or genotoxic risk to humans.

Evaluation of international assessments of glyphosate

The JMPR, EFSA, ECHA and Health Canada assessments of glyphosate all evaluated the publicly available data that was considered in the IARC monograph, as well as other published and unpublished data not available to IARC. In addition, the NZ EPA assessed the publicly available data contained in the IARC monograph and assessments by JMPR and EFSA.

Carcinogenicity studies in laboratory animals: EFSA concluded that the weight-of-evidence is that there is no carcinogenic risk to humans related to the use of glyphosate. JMPR concluded that glyphosate is not carcinogenic in rats but was unable to exclude the possibility that glyphosate is carcinogenic in mice at very high doses. The assessment conducted by ECHA concluded that there was no evidence of carcinogenicity in mice or rats due to a lack of statistical significance in pair-wise comparisons, a lack of consistency across studies, that slightly increased tumour incidences were only evident at doses exceeding the maximum tolerated dose, the absence of early cellular changes or pre-neoplastic lesions and/or incidences that tumour incidences were in the range of normal biological variation. Health Canada concluded that there was no evidence that glyphosate was carcinogenic or genotoxic in rats but that there was some evidence for a marginal increase in the incidence of ovarian tumours in mice only at the highest tested dose—however, these results were considered to be of low concern for human health risk assessment. The assessment commissioned by the NZ EPA concluded that long-term carcinogenicity studies produced consistently negative results and that the IARC assessment attributed inappropriate weight to the studies included in its assessment, which did not demonstrate a dose-response relationship, reported only minor positive results at the maximum dose tested, did not to consider relevant historical control data and excluded some studies that did not report positive associations between glyphosate exposure and carcinogenicity.

Genotoxicity studies: JMPR concluded that the overall weight-of-evidence is that glyphosate is unlikely to be genotoxic to humans at anticipated dietary exposures. EFSA, ECHA, Health Canada and the NZ EPA similarly concluded that the weight-of-evidence does not support the hypothesis that glyphosate is genotoxic. Again, these assessments concluded that the evidence presented by IARC as representative of strong evidence for genotoxicity and oxidative stress was primarily based on exposure scenarios not relevant to humans.

Epidemiological studies: ECHA concluded that the value of the human data for hazard classification purposes is questionable and limited because it is difficult to distinguish between the effects of the active constituent and co-formulants, as humans are never exposed to the active constituent alone, and humans are exposed to a many environmental chemicals, making it difficult to attribute health effects to one specific chemical. The JMPR, EFSA, ECHA and NZ EPA assessments concluded that while there was some evidence of a positive statistical association between glyphosate exposure and the risk of non-Hodgkin's lymphoma (NHL) in some retrospective

case-control studies, the one large, high-quality prospective cohort study found no statistical association at any exposure level. The EFSA assessment further noted that it was not possible to differentiate between the effects of glyphosate and the co-formulants in the epidemiological data available. The ECHA assessment describes a number of papers that did not identify a risk between glyphosate exposure and various specific cancer types, including NHL, lymphomas in general or multiple myeloma. The ECHA concluded that a comprehensive review of epidemiological studies assessing the possible association between glyphosate exposure and cancer found no consistent pattern of positive associations that would suggest a causal relationship between glyphosate exposure and the development of cancer in adults or children. The ECHA further concluded that, while epidemiological data is of limited value for detecting the carcinogenic potential of a pesticide, the data do not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type. The Health Canada assessment concluded that the majority of epidemiological data considered by IARC lacked adequate characterisation of glyphosate exposure and that as a result these studies were of limited use for supplementing the hazard assessment of glyphosate.

Assessment of adverse experience reports (AER)

Between 1996 and 2013, a total of four AERs relating to human safety were submitted to the APVMA's Adverse Experience Reporting Program (AERP). All were classified as 'possible' or 'probable' by the APVMA. Of the four reports, one was of skin irritation while the remaining three were reports of eye irritation. The APVMA is confident that the current safety and use directions included on approved labels for products containing glyphosate are sufficient to mitigate these known adverse effects.

Proposed regulatory position

Based on this nomination assessment, the APVMA concludes that the scientific weight-of-evidence indicates that:

- exposure to glyphosate does not pose a carcinogenic or genotoxic risk to humans
- there is no scientific basis for revising the APVMA's satisfaction that glyphosate or products containing glyphosate:
  - would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
  - would not be likely to have an effect that is harmful to human beings
  - would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
  - would be effective according to criteria determined by the APVMA by legislative instrument, and
  - would not unduly prejudice trade or commerce between Australia and places outside Australia.
- **there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration**
- the APVMA will continue to maintain a close focus on any new assessment reports or studies that indicate that this position should be revised.

1 INTRODUCTION

Glyphosate [*N*-(phosphonomethyl)glycine) is an aminophosphonic analogue of glycine, which is a naturally occurring amino acid. Glyphosate is classified as an organophosphate as it contains carbon and phosphorous; however, it does not affect the nervous system the way other organophosphates do. Glyphosate is a broad-spectrum, non-selective, post-emergent, systemic herbicide that kills or suppresses all plant types, except those that have been genetically modified to be resistant to glyphosate, and can be used as a plant-growth regulator/desiccator at lower dose rates. Herbicide products that contain glyphosate are commonly used to control annual and perennial broadleaf and grassy weeds in various agricultural and non-agricultural settings. Glyphosate binds strongly to soil particles and is readily metabolised by soil microorganisms, therefore when applied post-emergence, glyphosate demonstrates no pre-emergence or residual activity.

The water solubility of technical-grade glyphosate acid can be increased by formulating it primarily as its isopropylamine salt, or less commonly as monoammonium, potassium, trimesium, monoethanolamine or dimethylammonium salts, or various combinations of those salts. Furthermore, commercial formulated products contain various non-ionic surfactants to facilitate uptake by plants. Some commercial formulations also contain other active constituents in an attempt to mitigate herbicide resistance.

Glyphosate is taken up by the leaves and other green parts of the plant and translocated to the entire plant systemically. As a result, glyphosate is capable of total destruction of the plant. Glyphosate binds to and blocks the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), thereby disrupting the shikimic acid pathway and preventing the plant from synthesising the essential aromatic amino acids required for protein biosynthesis (phenylalanine, tyrosine and tryptophan), killing the plant. As this pathway is unique to plants and therefore is not present in mammals, glyphosate demonstrates low vertebrate toxicity.

The first product containing glyphosate was registered for use in Australia in the 1970s, under the trade name 'Roundup'. Products containing glyphosate that are registered for use in Australia are formulated as solutions, granules, aerosols and gels (Table 1) and can be applied using ground or aerial equipment, as well as some specialised application methods (eg aerosol).

1.1 Current regulatory status of glyphosate in Australia

As of February 2016 there were 80 active constituent approvals for glyphosate and 471 registered products containing glyphosate. Of the 471 registered products, 130 are for home garden use and 370 are for commercial/agricultural use (Table 1). In these registered products, glyphosate is present at varying concentrations and is formulated in various salt forms, including ammonium, dimethylammonium, isopropylamine, mono-ammonium, monoethanolamine and potassium salts. Some registered products contain additional active constituents, including amitrole, ammonium thiocynate, butafenacil, carfentrazone-ethyl, diflufenican, imazapyr and oxyfluorfen.

Glyphosate is approved for use in Australia to control various annual and perennial broadleaf, grassy and woody weeds, trees and brush and is used in a variety of different situations, such as:

- croplands for the control of emerged weeds prior to crop and fallow establishment, minimum tillage farming, direct drilling into seedbed, for pre-harvest desiccation

- non-cultivated land (eg industrial, commercial, domestic and public service areas) and rights of way
- forests, orchards, vines and plantations
- home garden use on rockeries, garden beds, driveways, fence lines, firebreaks, around buildings and prior to planting new lawns and gardens
- aquatic areas (restricted to dry drains and channels, dry margins or dams, lakes and streams)
- aquatic weed control and control of weeds on margins of dams, lakes and streams or in channels, drains or irrigation (selected products only).

Glyphosate is applied by ground boom, knapsack/handgun, gas/splatter gun, wiper equipment, controlled droplet application equipment, aerial spraying, aerosol spray, ready to use spray bottle and ready to use gel dispenser.

Table 1: Formulation types for glyphosate products

Formulation type	Level of active constituent	Product type
Aqueous concentrate	3.6 g/L	Home garden
	7.2 g/L	Home garden
	60 g/L	Commercial
	100 g/L	Home garden
	150 g/L	Commercial
	300 g/L	Commercial
	360 g/L	Home garden and commercial
	450 g/L	Home garden and commercial
	470 g/L	Commercial
	480 g/L	Commercial
	490 g/L	Home garden and commercial
	500 g/L	Home garden and commercial
	510 g/L	Commercial
	540 g/L	Home garden and commercial
Soluble concentrate	7.2 g/L	Home garden
	15.2 g/L	Home garden
	143 g/L	Home garden
	150 g/L	Commercial

Formulation type	Level of active constituent	Product type
	360 g/L	Home garden and commercial
	450 g/L	Commercial
	470 g/L	Commercial
	480 g/L	Commercial
	490 g/L	Home garden
	495 g/L	Commercial
	500 g/L	Commercial
	510 g/L	Commercial
	517 g/L	Commercial
	535 g/L	Commercial
	540 g/L	Home garden and commercial
	570 g/L	Commercial
	600 g/L	Commercial
Emulsifiable concentrate	360 g/L	Commercial
Suspension concentrate	225 g/L	Home garden and commercial
	360 g/L	Home garden and commercial
	450 g/L	Commercial
	510 g/L	Commercial
	600 g/L	Commercial
	700 g/L	Commercial
Water dispersible granule	680 g/kg	Home garden and commercial
	690 g/kg	Commercial
	700 g/kg	Commercial
	835 g/kg	Commercial
Water soluble granule	680 g/kg	Commercial
	700 g/kg	Commercial
	720 g/kg	Commercial

Formulation type	Level of active constituent	Product type
	800 g/kg	Commercial
	840 g/kg	Commercial
	900 g/kg	Commercial
	875 g/kg	Commercial
Aerosol	10 g/kg	Home garden
Liquid	7.2 g/L	Home garden
	360 g/L	Home garden and commercial
	450 g/L	Commercial
Liquid concentrate	570 g/L	Commercial
Emulsion, oil in water	4.8 g/L	Home garden
	25.6 g/L	Home garden
	432 g/L	Commercial
Gel	7.2 g/L	Home garden
	40 g/L	Home garden
Dry flowable	225 g/L	Home garden
Other liquids to be applied undiluted	7.2 g/L	Home garden
	7.4 g/L	Home garden
	16 g/L	Home garden

Previous reconsideration of glyphosate by the APVMA in 1996

A formal reconsideration of glyphosate was initiated following concern by the then Commonwealth Environment Protection Agency that certain surfactants in glyphosate formulations were acutely toxic to tadpoles at concentrations that are likely to occur in shallow water when products were used according to approved label instructions. Seventy five products were placed under review and all 27 holders were invited to provide information to the APVMA (then the National Registration Authority; NRA) relating to the review.

The scope of the review was limited to:

- reviewing application methods of glyphosate formulations adjacent to aquatic environments of all registered agricultural products

- a proposal to include a warning statement on all agricultural glyphosate product labels precluding use on or adjacent to waterways unless otherwise authorised
- a proposal to only allow use of glyphosate formulations in sensitive aquatic situations where it can be demonstrated that there is no significant risk to the aquatic environment.

The conclusions of the reconsideration were that the aquatic toxicity of registered glyphosate formulations was undesirably high and was mainly due to the surfactants in the formulations. Therefore, a number of conditions of registration were modified to describe more clearly the situations in which products registered for use in aquatic situations could be used to avoid the risk of significant aquatic contamination. Use of the formulated products was restricted to dry drains and channels and dry margins of dams, lakes and streams. Warning statements on labels were amended to minimise any possible aquatic contamination. Only formulations with an acceptable margin of aquatic safety would be registered for controlling weeds growing in or over water. Holders were provided 12 months (until 30 June 1997) to make the necessary changes to their products. No changes were made to products registered solely for home garden use, as the risk of significant aquatic contamination was considered very low. The final reconsideration report is available on the APVMA website.

Response to claims that glyphosate is responsible for causing birth defects

In June 2011, Earth Open Source (EOS) published a document titled 'Roundup and birth defects: is the public being kept in the dark?' In this document, EOS questioned the safety of glyphosate and products that contain it. The claims made by EOS were:

- exposure to concentrations of glyphosate lower than those commonly used in agriculture and the home garden have been linked to developmental malformations affecting the skull, face, brain and spinal cord in frog and chicken embryos
- a range of developmental malformations, as well as endocrine disruption and reproductive toxicity have been observed in humans and experimental animals following exposure to glyphosate
- a variety of *in vitro* test systems have demonstrated that glyphosate can induce damage to DNA and genetic material in laboratory animals and humans
- glyphosate exposure has been linked to cancer of the testis in rats, skin cancer in mice and blood system cancers in humans
- glyphosate exposure has been linked to neurotoxicity and the development of Parkinson's disease in humans.

The APVMA commissioned an expert review of that document, which was published in July 2013, to address the concerns raised in the EOS article. In doing so, the APVMA evaluated both the published studies cited in the EOS document and other more recent publications and archived toxicology studies of glyphosate, compared the EU reviews of glyphosate with reviews prepared by other regulators, assessed the scientific merit of the claims made by EOS and the research upon which those claims were based and considered whether there were implications for the registration of products containing glyphosate in Australia. The full review of the EOS document can be found on the APVMA archive website.

A number of conclusions were made in the review of the EOS document. These included:

- The available data do not indicate that glyphosate products registered for use in Australia and used according to label instructions present any unacceptable risks to human health, the environment or trade.
- The weight- and strength-of-evidence demonstrate that glyphosate is not genotoxic, carcinogenic or neurotoxic.
- Developmental malformations caused by glyphosate in toad and chicken embryos are not predictive of a developmental hazard to humans because of the routes of administration used. Some studies have reported fetal skeletal abnormalities, toxicity to the male reproductive tract during puberty and interference with the maturation of the male reproductive organs during puberty; however, these studies were affected by flawed design, methodology and/or reporting and the claimed effects on puberty are inconsistent.
- Glyphosate is extremely unlikely to cause reproductive or developmental toxicity in humans under normal conditions of exposure.
- At present, there is no scientific justification for classifying glyphosate as an endocrine disrupter.
- Effects on hormonal regulation and cellular toxicity observed *in vitro* may have been confounded by surfactants present in formulated products.
- Most studies utilising formulated products containing glyphosate have not identified which chemical constituent was responsible for causing the reported effects, or characterised their mode of action.
- The toxicological studies cited by EOS do not demonstrate a need to revise the current Australian Acceptable Daily Intake (ADI) of 0.3 mg/kg bw/day for glyphosate.
- New information that emerges from the United States (US) and Canadian reviews of glyphosate will be considered by the APVMA.

The Poisons Standard (SUSMP)

The Poisons Standard, or the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) controls how medicines and poisons are made available to the public and classifies them into Schedules according to the level of regulatory control that is required in order to maintain public health and safety. Scheduling of medicines and poisons in Australia is a legislative requirement administered by the Therapeutic Goods Administration (TGA). However, the scheduling controls are implemented through State and Territory legislation, therefore the implementation of any restrictions imposed by the TGA may differ between States and Territories. Model provisions about packaging and labels, a list of products recommended to be exempt from the provisions and recommendations about other relevant controls are also included.

When making a scheduling decision, various criteria are considered, including toxicity, purpose of use, potential for abuse, safety in use and the need for the substance. Medicines and poisons are classified in one of ten Schedules. Agricultural, domestic and industrial poisons are generally listed in Schedules 5 (caution), 6 (poison) or 7 (dangerous poison), which represent increasingly stricter container and labelling requirements. Products for domestic use must not be listed in Schedule 7.

Glyphosate is classified as a Schedule 5 (caution) substance, which is defined as a substance with a 'low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with strong warnings and safety directions on the label'. To classify as a Schedule 5 poison, the substance must adhere to the following criteria:

- the substance is non-corrosive and has a low toxicity
  - acute oral toxicity (rat): 2000 mg/kg to 5000 mg/kg
  - acute dermal LD_{50}: > 2000 mg/kg
  - acute inhalation LC_{50} (rat): > 3000 mg/m^3 (4 hours)
- the substance has a low health hazard from repeated use and is unlikely to result in irreversible toxicity
  - no other significant toxicity (eg carcinogenicity, mutagenicity, etc)
- the substance is capable of causing only minor adverse effects to humans in normal use
  - specialised personal protective equipment should not be necessary for safe use
- the likelihood of injury during handling, storage and use can be mitigated through appropriate packaging and label warnings
- the substance has a low potential for causing harm
  - potential harm is reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

1.2 Health-based guidance values for glyphosate

Health-based guidance values are established by regulatory authorities (and international bodies such as the JMPR) for the purpose of determining whether human exposure (via the diet or occupationally) to a particular chemical is safe. Health-based guidance values provide quantitative information to risk managers to enable them to make informed, scientific decisions related to protecting human health.

Acceptable Daily Intake (ADI)

The ADI is the amount of a chemical that can be ingested daily over a lifetime without any appreciable risk to health. The ADI is based on the lowest NOAEL (No Observed Adverse Effect Level) for the most sensitive adverse effect relevant to humans.

The ADI for glyphosate in Australia is 0.3 mg/kg bw/day based on the No-Observed-Adverse-Effect Level (NOAEL) of 30 mg/kg bw/day (the highest tested dose) in a 3-generation reproduction dietary study in rats and using a 100-fold safety factor to account for extrapolation from animals to humans as well as variation in sensitivity within the human population.

Acute Reference Dose (ARfD)

The ARfD is an estimate of the amount of a substance in food and drinking water, expressed on a milligram per kilogram bodyweight basis, which can be ingested in a period of 24 hours or less without appreciable health risk to the consumer. In 1998, JMPR concluded that an ARfD must be determined for all pesticides, unless the toxicological profile indicated that the pesticide was unlikely to present an acute hazard. As the toxicology assessments of glyphosate indicate that there is no likelihood of glyphosate presenting an acute hazard to human health, an ARfD has not been established for glyphosate in Australia or overseas.

Maximum Residue Limits (MRL) and National Residue Survey (NRS)

The maximum amount of a chemical that is legally permitted in a food is known as the MRL. The MRL is based on good agricultural and chemical use practices to ensure that an agricultural or veterinary chemical has been used according to the directions on the approved label. The MRL is set well below the level that would result in the health-based guidance values being exceeded if the chemical is used according to the approved label instructions. Therefore, while exceedance of the MRL may indicate a misuse of the chemical, it does not normally indicate that there is a public health or safety concern. The APVMA sets MRLs for agricultural and veterinary chemicals in agricultural produce. The states and territories are responsible for enforcing MRLs.

The *Agricultural and Veterinary Chemicals Code Instrument No. 4 2012* (MRL Standard) lists MRLs for chemicals that may arise from the approved use of products containing that chemical, and outlines the definitions of those residues. The glyphosate residue definition is the sum of glyphosate, *N*-acetyl-glyphosate and aminomethyphosphonic acid (AMPA) metabolite, expressed as glyphosate.

As a part of the Department of Agriculture and Water Resources strategy to minimise chemical residues in agricultural product, the NRS facilitates testing of animal and plant products for pesticide and veterinary medicine residues, and environmental contaminants. In the 2013–14 NRS report, glyphosate residues greater than half of the MRL were not detected in any samples of barley, canola, chickpea, faba bean, field pea, lentil, lupin, maize, sorghum, triticale, wheat, wheat durum or macadamias. In 1/28 samples of oats, glyphosate residues above the MRL were detected (NRS 2014b), while in 1/37 almond samples, glyphosate residues lower than the MRL were detected (NRS 2014a). In the 2014–15 report (not yet published), glyphosate residues above the MRL were reported in 1/42 oat samples and residues below the MRL (above half of the MRL) were reported in 4/42 oat samples (NRS 2015). No residues greater than half of the MRL were detected in any samples of barley, chickpea, faba bean, canola, cowpea, field pea, lentil, maize, lupin, maize, mung bean, sorghum or wheat.

Australian Total Diet Study (ATDS)

The ATDS is coordinated by FSANZ to monitor Australia's food supply and ensure that food regulatory measures are protecting consumer health and safety. The ATDS assesses dietary exposure to pesticide residues, contaminants and other substances and is conducted approximately every two years.

The 23rd ATDS examined dietary exposure to 214 agricultural and veterinary chemicals, nine contaminants, 12 mycotoxins and 11 nutrients in 92 commonly consumed foods and beverages in 2008 (FSANZ 2011a). Glyphosate residues were detected in 2/12 samples of multigrain bread (mean concentration 0.016 mg/kg) (FSANZ 2011b). Based on these results, FSANZ estimated the mean consumer dietary exposure to glyphosate as 0.12, 0.81, 0.87, 0.97 and 1.4 µg/day in children aged 9 months, 2–5 years, 6–12 years and 13–16 years and adults aged 17 years and above, respectively (FSANZ 2011b). These estimated exposures are well below (214–25 000 times) the ADI of 0.3 mg/kg indicating that there are no safety concerns for Australian and New Zealand consumers.

Drinking water standards

The Australian Drinking Water Guidelines (the Guidelines) are a joint publication of the National Health and Medical Research Council (NHMRC) and the Agricultural and Resource Management Council of Australia and New Zealand. The Guidelines are not legally enforceable but provide a standard for water authorities and state health authorities to ensure the quality and safety of Australia's drinking water.

The health-related guideline value (expressed as mg/L) is the concentration or measure of a water quality characteristic that, based on present knowledge, does not result in any significant risk to the health of the consumer over a lifetime of consumption (NHMRC 2011). Health values are derived so as to limit intake from water alone to approximately 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult having a daily water consumption of 2 litres over a lifetime. The current health-related guideline value for glyphosate in drinking water is 1 mg/L—excursions above this value would need to occur over a significant period of time to be of a health concern (NHMRC 2011). Glyphosate is generally not reported in the analysis of Australian waters and is unlikely to be found at levels that may cause health concerns.

1.3 Legislative basis for a reconsideration of glyphosate

The basis for a reconsideration of the registration and approvals for a chemical is whether the APVMA is satisfied that the safety, efficacy and trade criteria listed in sections 5A, 5B and 5C of the Agvet Code for continued registration and approval are being met. These requirements are that the use of the product, in accordance with instructions approved, or to be approved, by the APVMA for the product or contained in an established standard:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
- would not be likely to have an effect that is harmful to human beings
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
- would be effective according to criteria determined by the APVMA by legislative instrument, and
- would not unduly prejudice trade or commerce between Australia and places outside Australia.

The APVMA may also consider whether labels for containers for chemical products containing glyphosate meet the labelling criteria as defined in section 5D of the Agvet Code which requires that labels have adequate instructions relating to:

- the circumstances in which the product should be used
- how the product should be used
- the times when the product should be used
- the frequency of the use of the product
- the re-entry period after use of the product
- the withholding period after the use of the product
- disposal of the product and its container
- safe handling of the product and first aid in the event of an accident
- any matters prescribed by the regulations.

2 INTERNATIONAL REGULATORY STATUS

Glyphosate is approved for use throughout the world, including in Europe and the United Kingdom (UK), the US, Canada, Australia, New Zealand, China, Brazil etc.

2.1 United States

The United States Environmental Protection Agency (US EPA) registers pesticides under the Federal Insecticide, Fungicide and Rodenticide Act and periodically (at least every 15 years) re-evaluates pesticides to ensure that they continue to meet registration standards, noting that new scientific information may be generated that should be taken into consideration. The registration of glyphosate is currently being reviewed as a part of this process. The re-assessment began in 2009 and was originally scheduled for completion in 2015; however, finalisation of the assessment was delayed following the re-classification of glyphosate by IARC. The final report is currently expected to be completed and published in 2016. The US EPA utilises a risk assessment process for evaluating the potential for health and ecological effects of a pesticide. The human health risk assessment process utilises the National Research Council's process for human health risk assessments, which is the procedure outlined by the International Programme on Chemical Safety (IPCS) and adopted by JMPR, as described in Section 4.3. In addition, the US EPA has developed a framework to incorporate epidemiological information into its risk assessment, which is based on peer-reviewed, robust principles and tools. The framework methodology was reviewed in 2010 by the Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel. Chemicals are assessed for carcinogenicity using the US EPA's Guidelines for Carcinogen Risk Assessment (2005).

In February 2016, the US Food and Drug Administration (US FDA) announced that they would begin testing for residues of glyphosate on various foods, including soybeans, corn, milk and eggs. Concurrently, the US Fish and Wildlife Service announced that they would commence an analysis in conjunction with the US EPA of the impacts of four commonly used pesticides (including glyphosate) on 1500 endangered species, which is due for completion by December 2022.

Glyphosate-based formulations are currently registered in the US to control weeds in various fruit, vegetable and other food crops, glyphosate-resistant transgenic crops, ornamental plantings, lawns and turf, greenhouses, aquatic areas, forest plantings and roadside rights of way. Products registered in the US that contain glyphosate are formulated as liquids, solids and ready-to-use formulations, and can be applied using ground and aerial equipment as well as small hand-held sprayers.

2.2 Canada

The registration of pesticides in Canada is regulated by Health Canada's Pest Management Regulatory Agency (PMRA). In 2010 Health Canada's PMRA commenced a re-evaluation of glyphosate in collaboration with the US EPA's re-evaluation of glyphosate. In April 2015, the PMRA published its Proposed Re-evaluation Decision (PRVD2015-01) for glyphosate. In that document, the PMRA proposed continued registration of products containing glyphosate for sale and use in Canada. However, as a condition of the proposed continued registration, new risk reduction measures were proposed for end-use products, aimed at protecting both human health and the environment (Table 2).

Table 2: New measures to minimise risk of glyphosate exposure proposed by Health Canada's Pest Management Regulatory Agency

Human health	Environment
A restricted-entry interval of 12 hours for agricultural uses to protect workers	Environmental hazard statements to inform users of toxicity to non-target species
Apply only when potential for drift to areas of human habitation or activity (eg houses, cottages, schools and recreational areas) is minimal, to protect bystanders	Spray buffer zones to protect non-target terrestrial and aquatic habitats
	Precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecast are proposed to reduce potential for runoff to adjacent aquatic habitats
	A vegetative strip between treatment area and edge of a water body to reduce runoff to aquatic areas

Following the publication of the proposed re-evaluation decision, the PMRA accepted written comments on the report for 60 days from the date of publication. The PMRA will consider all submissions prior to making a final, scientific decision on the registration of glyphosate in Canada.

2.3 Europe and the United Kingdom

All active constituents used in pesticide products in the EU are subject to approval by the European Commission (EC). However, individual Member States are responsible for authorising the final formulated pesticide products containing those active constituents in its territory. Therefore, whilst a chemical may be registered for use in the EU, Member States have the power to restrict use of that product in its territory. The EC approval is limited to a maximum of ten years—therefore, if manufacturers wish to continue using that active constituent in pesticide products, they must apply for renewed approval prior to the end of these ten years. The EC appoints a member state to act as the Rapporteur Member State (RMS) to conduct the assessment of a chemical.

The European Food Safety Authority (EFSA) is an agency that is funded by the EU but operates independently of the European legislation and member states. Legally established in 2002 by the EU, EFSA provides scientific advice and communication on risks associated with the food chain in Europe and is responsible for risk assessment of available science, but is not involved in legislative risk management or policy determination. Instead, the risk assessment conducted by EFSA is used to inform European policy and legislation by the EU risk managers, including the EC and the European Parliament (EP).

Glyphosate is registered for use throughout Europe and the UK and in August 2014 was subjected to a re-assessment by the RMS, Germany, as mandated by the EC and coordinated by EFSA. The Federal Republic of Germany was appointed as the RMS to conduct the assessment. The Federal Office of Consumer Protection and Food Safety was appointed by the German government as the lead authority for drafting the Renewal Assessment Rapport (RAR). The Federal Institute for Risk Assessment (BfR) was subsequently commissioned to assess the potential health risks of glyphosate. Once completed, the draft report was presented to EFSA and a consultation

period commenced. All comments and additional data resulting from the consultation period was incorporated into the draft, which was then submitted to EFSA in December 2014.

In February 2015, the BfR prepared a revised health risk assessment report on glyphosate, which was subsequently revised in April 2015 to include additional evaluation tables and clarify some factual information following consultation with EFSA. The assessment by EFSA was published in November 2015. The report concluded that glyphosate was 'unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential' (EFSA 2015).

In April 2015, the EC provided EFSA with a second mandate, to consider the findings of the IARC regarding the potential carcinogenicity of glyphosate or products containing glyphosate in the original assessment. In July 2015, the German government and EFSA commissioned BfR to review the IARC monograph on the re-classification of glyphosate. The review was completed in August 2015 as an addendum to the original RAR and was peer reviewed by EFSA. A detailed discussion of the BfR's review of the IARC monograph is provided below in Section 4.4).

Briefly, the BfR agreed with IARC's conclusion that there is 'limited evidence in humans for the carcinogenicity of glyphosate' but noted that no consistent positive association between glyphosate exposure and the development of cancer was demonstrated, and the most powerful study reported no effect. The BfR disagreed with IARC's conclusion that there is 'sufficient evidence in animals for the carcinogenicity of glyphosate', concluding that the weight-of-evidence suggests that there is no carcinogenic risk related to the use of glyphosate and that no hazard classification for carcinogenicity is warranted according to the Classification, Labelling and Packaging of Substances and Mixtures (CLP criteria) (Germany 2015). The BfR also disagreed with IARC's conclusion that there 'is mechanistic evidence for genotoxicity, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and cell proliferation or death of glyphosate' and concluded that the mechanistic and other studies do not provide evidence for a carcinogenic mechanism. The BfR concluded that the weight-of-evidence suggests that neither glyphosate nor AMPA (a metabolite of glyphosate) induce mutations *in vivo* and that no hazard classification for mutagenicity was warranted according to CLP criteria (Germany 2015).

The initial registration of glyphosate was scheduled to expire on 31 December 2015 (EC 2015). Following an expert meeting of EFSA, the EU member states, WHO, IARC and the US EPA, and in consideration of the revised RAR and addendum, EFSA completed its report for the assessment of glyphosate for the purpose of renewed approval and recommended that a renewal of the registration of glyphosate be granted. The EFSA RAR and addendum were subject to a thorough peer review by the competent authorities of the EU Member States and to accommodate that peer review process, the registration of glyphosate was provisionally extended until 30 June 2016. All but one of the Member States experts agreed that glyphosate is unlikely to be genotoxic or pose a carcinogenic risk to humans. The EC postponed a vote by EU member states to renew approval of glyphosate, which was originally scheduled for the meeting on 7 and 8 March 2016 of the EU Standing Committee on Plants, Animals, Food and Feed (hereafter referred to as the Standing Committee) until after the European Parliament vote in April 2016.

In March 2016, the EU Environment Committee Members of the European Parliament (MEPs) voted in favour of a resolution for the EC to abandon its proposal to renew approval of glyphosate in the EU for a further 15 years with no restrictions. The Environment MEPs instead requested that the EC conduct an independent review and disclose all of the scientific evidence used by EFSA in its assessment of glyphosate. They added that the EU Food and Veterinary Office should also be mandated to test and monitor glyphosate residues in food and drink.

The resolution was put to a vote at the plenary session of the EP scheduled for 11–14 April in Strasbourg, which again resulted in a postponement of the vote to re-register glyphosate, as a qualified majority consensus could not be reached. The Standing Committee again met on 18–19 May 2016 to discuss a 10 year re-registration for glyphosate in the EU. Again, the vote was postponed because a qualified majority was not reached. On 2 June 2016, the EC announced a proposal for the Standing Committee to meet on 6 June 2016 to consider a 2-year extension to the current registration of glyphosate so that the ECHA could complete an assessment of the carcinogenicity and potential for endocrine disruption of glyphosate. The EC also proposed banning polyethoxylated tallow amines (POEA; in glyphosate-based formulations only), minimising the use of glyphosate in public parks, playgrounds and gardens, and minimising pre-harvest use of glyphosate. In order for the proposal to pass, 55% of Member States (representing 65% of the EU's population) would be required to vote in favour. Of the 28 Member States, 20 voted in favour of the proposal, 7 abstained (did not vote for or against) and 1 (Malta) voted against the proposal. As a result of the relatively large populations of some of the countries that abstained from voting, the favourable votes accounted for only 52.91% of the EU's population and the proposal did not pass.

On 24 June 2016, the EC convened an Appeals Committee to consider the re-approval of glyphosate for 18 months to allow the ECHA to gather additional data and undertake a comprehensive analysis of the health risks association with its use. Again, a qualified majority position was not reached, with 19 countries in favour of the extended approval, two against (France and Malta) and seven abstaining, representing 51.49% of the EU's population in favour of the extension.

When a qualified majority is not obtained, the EC may bring forward its own decision to authorise the re-approval of a chemical. On 29 June 2016, the EC extended the approval of glyphosate in the EU to allow the ECHA to complete its assessment of glyphosate. This approval will expire either 6 months following the date of receipt of the ECHA report or 31 December 2017, whichever occurs first (EC 2016). On 11 July 2016, Member State experts voted as a qualified majority in favour of two recommendations proposed by the EC as conditions to the registration extension, at a meeting of the Standing Committee in Plants, Animals, Food and Feed. These restrictions included:

- an EU-wide ban on POEAs contained in some glyphosate-based formulations
- restricted use of glyphosate-based formulations in public parks, playgrounds and home gardens and for pre-harvest application.

In July 2016, the pesticide regulator in Malta (the Malta Competition and Consumer Affairs Authority) began implementing a policy decision by the Environment Ministry to withdraw authorisation for all glyphosate and glyphosate-based formulations.

Glyphosate is currently authorised throughout the EU and UK, predominantly for uses in agriculture (cereals, vineyards, olives, citrus, nuts etc), but also to manage weed growth on non-cultivated areas (eg railway tracks, verges), public amenities, forestry and aquatic environments, and in home gardens. Glyphosate is authorised for weed control use after harvest or sowing, before a new crop is planted. Glyphosate is also authorised for pre-harvest weed control use and dessication (to promote the maturation of crops) in crops such as oilseed rape and cereals. It is not currently clear which uses will be affected as a result of the recently announced use restrictions described above.

2.4 New Zealand

In New Zealand, the registration of herbicides is the responsibility of the Environmental Protection Authority and the Ministry for Primary Industries. Glyphosate is listed on the Chief Executive Initiated Reassessment (CEIR) Programme and as such is being actively monitored by the Environmental Protection Authority.

Glyphosate has been registered in New Zealand since 1976 and is used in various settings, including orchards, vineyards, pastures, vegetable patches, along roadways and in parks, sporting fields and home gardens.

3 EVALUATION METHODOLOGY: THE WEIGHT OF SCIENTIFIC EVIDENCE

Consistent with the scientific method, a weight-of-evidence approach should be used to determine whether a chemical is carcinogenic. To conduct an initial quality assessment of each individual study, the study design should be assessed, taking into account OECD (Organisation for Economic Co-operation and Development) or national test guidelines where appropriate. In a weight-of-evidence assessment, any observation should be reproducible: the strength of any finding will be increased if it can be replicated under the same conditions in more than one laboratory. Plausible patterns in the hierarchy of the results will also strengthen the finding—ie where a finding *in vitro* is reproduced *in vivo.*

In toxicological science, there are a number of criteria that are used to determine whether an effect, such as cancer, is treatment-related and adverse:

- *Dose-response relationship*—the number of animals or subjects showing the effect and/or the severity of the effect should increase with dose. There should be a progression to a more severe state of toxicity as the dose and duration of dosing increases.
- *Consistency of the effect*— the effect should be observed consistently across studies of similar exposure duration and sexes (in unusual cases an effect may be sex-specific). Additionally, an effect should be corroborated by related toxicological endpoints – for example, increases in malignant neoplasms should be preceded by cellular changes that should be observed at lower doses or following shorter exposure durations.
- *Statistical significance*—differences between treated groups and the concurrent control group should be statistically significant. However, statistical significance on its own does not imply biological significance and the absence of statistical significance also does not necessarily mean the absence of an effect (for example a rare type of tumour may be highly biologically relevant).
- *Biological plausibility*—an observed effect needs to be mechanistically plausible based on the characteristics of the chemical and principles of biology/physiology.
- *Natural variation and incidental findings*—the normal range of natural variation of a parameter in the test species needs to be understood through the use of age- and sex-matched historical control data. All laboratory animal strains used in rodent bioassays have a background incidence of age- and sex-related neoplasms at different tissue sites. It is critical that this normal range of biological variation is documented and understood.

When assessing toxicological data associated with chemical residues in food, the APVMA has regard to the principles and methods outlined by the IPCS, described below in Section 4.3 (IPCS 2009) including guidance on the interpretation of toxicological data by JMPR[1] and OECD[2]. For the evaluation of carcinogenicity via dietary or other exposure routes, the IPCS has published a mode-of-action (MOA) framework for chemical carcinogenesis (Meek et al 2013). In this framework, treatment-related cancer must first be demonstrated in laboratory animals

[1] http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1
[2] http://www.oecd-ilibrary.org/docserver/download/9750321e.pdf?expires=1472172141&id=id&accname=guest&checksum=28F68D5204F38A1B96055A611D12C4DF

before proceeding to examine genotoxicity data, human epidemiological and mechanistic data in order to determine the mechanism for how cancer arises and the human relevance of adverse effects observed in laboratory animals.

The APVMA considered aspects of study design and reporting that may either increase or decrease confidence in the data. The presence of a dose-response relationship, consistency and reproducibility were considered to increase confidence in the data, while any unexplained inconsistencies and significant deviations from international test guidelines were considered to reduce confidence in the data. Therefore, those studies that demonstrated a dose-response relationship, adhered to international test guidelines (where appropriate) and were consistent and reproducible within and/or between laboratories were given more weight in the assessment.

For epidemiological data, the APVMA considered prospective cohort studies to be more powerful than retrospective case-control studies, which are more prone to recall bias and confounding by exposure to other chemicals and environmental situations. It is well known that study participants' memory may not be reliable: participants are often asked to provide information about use patterns that occurred many years previously, participants may be providing information relating to a family members' usage (not their own) and it is possible that a participant with cancer may have spent more time thinking about possible causes and exposure scenarios than participants without cancer. It is also very difficult to separate usage of one pesticide from another: those who routinely use glyphosate-based formulations are likely to have been using many other types of agricultural and/or industrial chemicals, or be exposed to other occupational scenarios that may confound the data.

3.1 Use of international test guidelines

All scientific studies considered by the APVMA are assessed on their scientific merits. However, studies that have been conducted according to principles of Good Laboratory Practice (GLP) and comply with international test guidelines are preferred because of the assurance of their scientific quality.

To ensure the scientific quality of studies submitted for regulatory purposes and to enable comparison of studies utilising the same methodology in different laboratories, a number of internationally accepted test guidelines have been developed for various toxicological studies. The testing guidelines produced by the OECD are commonly used throughout the world and provide quality standards for different types of studies. Guidance is provided regarding test species and strain, the number of animals to be used, choice of chemical doses and duration of exposure, as well as parameters to be measured, observed and reported. By comparing studies that were conducted using equivalent test guidelines, regulators can identify potential human health hazards and set appropriate endpoints for risk assessment and management.

When assessing toxicology studies, consistency with international test guidelines is not the only measure of scientific quality. For some types of studies, guidelines have not yet been developed while for studies that were never intended for regulatory or risk assessment purposes (eg most studies published in scientific journals) some criteria may rarely be met. However, depending on how the study design, interpretation or reporting differs from the guidelines, the discrepancies may not affect the validity of the results. Specifically, data for individual animals is rarely reported in scientific publications; instead the data is presented as group means along with a measure for variance between control and treatment groups. This omission would not be considered a serious flaw and invalidate the study results. However, other elements of the testing guidelines may be considered more critical and omission may invalidate the study findings. For example, failure to independently code slides (or failure to report independent coding) used to visually score assay results would be considered as a potentially critical flaw, as it

would not be clear that the scoring was performed by an independent observer who was not aware of the treatment or control group being scored. In other cases, test guidelines may stipulate a maximum dose that is associated with minimal toxicity, for determining a specific carcinogenic or genotoxic end-point. In some experimental studies, that maximum dose may be exceeded up to ten-fold. In the absence of appropriate cytotoxicity tests, it may not be possible to determine whether any positive effects are indeed indicative of genotoxicity.

3.2 Statistical significance and biological or toxicological relevance

Statistical analysis is a useful tool for detecting differences between groups exposed to a test compound or not. Biologically this difference may be real or a chance or incidental finding. That is why a statistically significant result on its own without an evaluation of its biological and ultimately toxicological relevance provides only limited insight into the possible effects of a chemical. As described above, there are a range of other criteria that must be met in order to conclude that an effect is truly treatment-related and adverse.

Epidemiological data is often presented using an Odds Ratio (OR) with an associated confidence interval (CI; usually 95%). An OR is a relative measure of effect and is used in this context to compare the incidence of cancer (or some other health outcome) in individuals exposed to glyphosate with those who have not been exposed. If the OR is 1, the statistical analysis implies that there is no difference between the incidences of cancer in either group. The CI is used to determine the level of uncertainty around the OR, because the sample population used in the study is only a representative group of the overall population. The statistical test infers that the true population effect lies between the upper and lower CI. Therefore, a very narrow CI infers that the true effect is very close to the estimated OR, while a wide CI infers that the OR is less reliable. In addition, if the CI crosses 1 (eg 0.5–1.5), the statistical test is inferring that there is no difference between the two groups, in terms of cancer incidence. Therefore, the APVMA considered studies reporting positive associations between glyphosate exposure and cancer incidence that presented an OR greater than 1 and a narrow CI range that did not cross 1 to be more powerful than studies that had a wide CI range that crossed 1.

3.3 Historical control data and spontaneous tumour incidence

Consideration of historical control data is an important aspect of interpreting toxicology studies. Historical control data is a compilation of the findings from strain-, age- and sex-matched control animals from all the studies undertaken by the performing laboratory and provides an indication of the background frequency of tumours that occur in that species/strain of animals by chance. A statistically significant increase in tumour frequency may be observed in treated animals when a lower than normal tumour frequency is observed in control animals in that study. Conversely, a non-significant result may be observed when a higher than normal tumour frequency is observed in the control group. Therefore, historical control data is used to determine whether an increase in tumours is within the realms of normal biological variation or is in fact truly treatment related. For some common tumours
(eg liver, pituitary or adrenal), the historical control ranges are so wide that the incidences of tumours in both the concurrent control and treated groups often fit within their bounds. In these cases, the mean value or distribution of historical control data may be more useful than the range only.

3.4 Test species and route of administration

Data obtained from humans is preferable to data obtained from experimental animals because it increases the certainty that an observed effect is relevant to humans. Volunteer studies and human clinical trials provide accurate exposure metrics that can be directly linked with adverse outcomes. However, the extent of exposure can be difficult to determine in human observational studies (such as epidemiological studies), because subjects are often expected to rely on memory recall to provide exposure details and subjects are frequently exposed to more than one chemical. When evaluating studies conducted using animal models, those that use mammals are considered more relevant to human outcomes than non-mammalian species or *in vitro* cell culture studies.

When evaluating the toxicological effects of pesticides, such as glyphosate, studies in which the chemical was administered via the oral (gavage, diet, drinking water), dermal or inhalational routes are highly relevant because these are the only possible routes of exposure for humans. Subcutaneous (skin injection), intravenous (vein injection) and intraperitoneal (stomach cavity injection) administration are generally not directly relevant for chemical risk assessment purposes because humans would not be exposed via these routes. In addition, these routes of exposure bypass normal metabolic processes.

4 SUMMARY OF ASSESSMENTS AND CONCLUSIONS

4.1 The IARC glyphosate monograph

The IARC is a specialist cancer agency of the WHO and, as such, follows the general governing rules of the United Nations. However, IARC has its own Governing Council and Scientific Council. Currently, 25 countries are IARC members, including Australia.

The IARC assessment process

The IARC appoints a Working Group to evaluate carcinogenic risks to humans, which is guided by the Preamble (IARC 2006). The Preamble is a statement of scientific principles; however, the procedures that each Working Group use to implement those scientific principles are not specified and are the prerogative of each individual Working Group. The Monographs produced by the Working Groups assess the strength of available evidence that an agent could alter the age-specific incidence of cancer in humans. Working Group members have usually published significant research related to the carcinogenicity of the agents being reviewed.

The IARC Monographs evaluate cancer hazards and the Preamble emphasises the distinction between a hazard and a risk. A cancer hazard is defined in the Preamble as 'an agent that is capable of causing cancer under some circumstances' while a cancer risk is defined as 'an estimate of the carcinogenic effects expected from exposure to a cancer hazard'. The Preamble cautions that the Monographs identify cancer hazards even when the risks are very low at current exposure levels (IARC 2006).

The IARC assessments also utilise a 'strength-of-evidence' approach, rather than the 'weight-of-evidence approach' more common in regulatory assessments. The weight-of-evidence approach assesses the predictive validity of a hypothesis, while the strength-of-evidence determines its level of extremeness (Simon 2014). Predictive validity is dependent on factors such as study design, sample size, background rates etc. A strength-of-evidence assessment may be based on a single study where the effect was easily noticeable or was apparent in a large population, even though the predictive value of the study was weak.

The IARC Preamble states that while the Monographs are used by regulatory authorities worldwide to make risk assessments and formulate regulatory decisions, they represent only one part of the body of information that informs regulatory decisions (IARC 2006). The Preamble acknowledges that public health options vary according to circumstance and geographical location and relate to a multitude of factors. As a result, the IARC does not regard regulation or legislation while developing Monographs, as it acknowledges that this is the responsibility of individual governments or other international organisations.

When assessing an agent for a Monograph, the Working Group reviews epidemiological studies, cancer bioassays in experimental animals, as well as exposure, mechanistic and other relevant data. In each case, the Working Group only considers data that has been determined by them to be relevant to the evaluation. Only reports that have been published or accepted for publication in the openly available scientific literature and data from government agency reports that are publicly available are reviewed (IARC 2006). Unlike regulatory authorities, IARC does not consider the often large number of unpublished studies submitted for regulatory assessment.

The outcome of the Working Group's assessment is a categorisation of an agent that reflects the strength-of-evidence from studies in humans and experimental animals and other relevant data. The classifications used by IARC and the circumstances that may lead to an agent being assigned to each group are listed below (IARC 2006):

- Group 1 – the agent is carcinogenic to humans
  - there is sufficient evidence of carcinogenicity in humans
  - evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence that the agent acts through a relevant mechanism of carcinogenicity in humans (exceptional circumstances)
- Group 2A – the agent is probably carcinogenic to humans
  - limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
  - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that carcinogenesis is mediated by a mechanism that also operates in humans
  - limited evidence of carcinogenicity in humans but the agent clearly belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2A (exceptional circumstances)
- Group 2B – the agent is possibly carcinogenic to humans
  - limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
  - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
  - inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals, as well as supporting evidence from mechanistic and other relevant data
  - strong evidence from mechanistic and other relevant data.
- Group 3 – the agent is not classifiable as to its carcinogenicity to humans
  - inadequate evidence of carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals
  - inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans (exceptional circumstances)
  - agents that do not fall into any other group.
- Group 4 – the agent is probably not carcinogenic to humans
  - evidence suggesting lack of carcinogenicity in humans and experimental animals
  - inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data.

Assessment of glyphosate by IARC

In March 2015, IARC evaluated the potential carcinogenicity of five organophosphate pesticides and classified glyphosate (as well as malathion and diazinon) as 'probably carcinogenic to humans', Group 2A. The complete monograph was published in July 2015. Note that where the Working Group cited an unpublished study, it relied on the published summary report as the complete, original study report was not available.

The Working Group concluded that there was 'limited evidence of carcinogenicity' in humans, with a positive association observed between exposure to glyphosate and NHL (IARC 2015). The IARC preamble explains that 'limited evidence of carcinogenicity' in humans is concluded when the Working Group has determined that a credible causal link between the agent and cancer may have been identified 'but chance, bias or confounding could not be ruled out with reasonable confidence' (IARC 2006). The Working Group also concluded that there was 'sufficient evidence of carcinogenicity' in experimental animals (IARC 2015). The IARC Preamble describes that sufficient evidence of carcinogenicity is concluded when a causal relationship between the agent and an increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms has been established in either two or more species of animals, or two or more independent studies in one species. Sufficient evidence is also considered to be established when an increased incidence of tumours is observed in both sexes of a single species in a well conducted study (preferably conducted according to GLP). Alternatively, sufficient evidence of carcinogenicity may be considered established in a single study in one species and sex when malignant tumours occur to an 'unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites' (IARC 2006).

The studies relied on by the Working Group for human carcinogenicity comprised reports of the Agricultural Health Study (AHS) and various case-control studies conducted in the US, Canada and Sweden. The Working Group concluded that these studies presented increased risks for the development of NHL associated with exposure to glyphosate (IARC 2015).

The AHS was a prospective cohort study of 54 315 licensed pesticide applicators from Iowa and North Carolina, which has produced data relating to the use of pesticides, such as glyphosate on the risk of cancer at various sites. Overall, the study concluded that exposure to glyphosate was not associated with all cancers combined (RR 1.0; 95% CI 0.90–1.2) or any cancer at a specific anatomical site (De Roos et al. 2005).

A study conducted in Canada reported an increased risk of NHL following more than 2 days per year of exposure to glyphosate in 51 exposed cases (OR 1.20; 95% CI 0.83–1.74 when adjusted for age, province and medical variables) (McDuffie et al. 2001); however, no adjustment for other pesticides was performed and the OR spans 1 (indicating that there was no difference between the incidence of cancer in either group). A study conducted in the US (De Roos et al. 2003) and two studies conducted in Sweden (Hardell & Eriksson 1999; Eriksson et al. 2008) reported an increased risk of NHL following glyphosate exposure, which persisted following adjustment for other pesticides. However, the results of Hardell & Eriksson (1999) should be treated with caution, as only 4 glyphosate-exposed cases and 3 controls were included and while an increased OR was reported (2.3), the 95% CI was wide (0.40–13.0), indicating poor precision and spans 1, indicating that there was no difference between the incidence of cancer in either group. Hardell et al. (2002) analysed pooled data that included the data presented in Hardell & Eriksson (1999)—a non-statistically significant elevated risk for NHL following glyphosate exposure with poor precision and an OR that spans 1 was identified (OR 1.86; 95% CI 0.55–6.20). In 29 exposed cases and 18 controls, Eriksson et al. (2008) reported an increased risk for NHL following more than 10 days/year exposure to glyphosate (OR 2.36; 95% CI 1.16–4.40) following adjustment for exposure to other pesticides. After pooling

data from three case-control studies of NHL conducted in the Midwest US in the 1980s, De Roos et al. (2003) reported an increased incidence of NHL following exposure to a number of individual pesticides, including glyphosate (OR 2.1; 95% CI, 1.1–4.0), based on 36 cases. However, while an increased risk was still identified following adjustment for exposure to other pesticides (OR 1.6, 95% CI 0.90–2.8), it was no longer significant. A case-control study also conducted among males in the Midwest US reported an increased risk of developing NHL for men who had ever farmed (OR 1.2; 95% CI, 1.0–1.5) and men who had ever handled glyphosate (OR 1.1; 95% CI, 0.7–1.9); however, no adjustment was made for other pesticides (Cantor et al. 1992). No association between glyphosate exposure and development of NHL was calculated in a hospital-based case-control study conducted in France (OR 1.0; 95% CI 0.5–2.2) (Orsi et al. 2009); however, only 12 exposed cases were assessed. One study conducted in Europe reported an elevated risk for B-cell lymphoma following glyphosate exposure (OR 3.1; 95% CI 0.6–17.1), but again, this study was based on few exposed cases (n=4) and controls (n=2), with a very wide CI (poor precision) that spans 1 and the authors of the paper concluded that no increased risk of either lymphoma overall, or B cell lymphoma was associated with glyphosate exposure (Cocco et al. 2013).

The Working Group also relied on three studies that reported an increased risk of multiple myeloma (a subtype of NHL) following more than 2 days glyphosate exposure per year (Brown et al. 1993; Orsi et al. 2009; Kachuri et al. 2013). However, none of these studies adjusted for the effect of other pesticides and in all three studies, the results were not statistically significant. Therefore, the variation observed in the results could be attributable to normal biological variation and not exposure to glyphosate or other pesticides. A report of data obtained by the AHS found no association between glyphosate exposure and NHL (OR 1.1; 95% CI 0.5–2.4; n=54 315) but saw an increased risk of multiple myeloma when the data were adjusted for multiple confounders, such as demographic and lifestyle factors, as well as other pesticides (OR 2.6; 95% CI 0.7–9.4; n=40 716) (De Roos et al. 2005). However, the number of myeloma cases included in the study was small (32 cases out of 2088 total cancer cases) and the wide CI spanning 1 indicates poor precision and a lack of difference between groups. Re-analysis of the data determined that the increased risk of multiple myeloma (OR 1.24; 95% CI 0.52–2.94) was only present in the subset of subjects for which there was no missing data (22 cases); however, again, the CI spans 1 (Sorahan 2015). This re-analysis of the data concluded that the observed increased risk of developing multiple myeloma following glyphosate exposure resulted from the use of an unrepresentative restricted dataset and that analysis of the full dataset provided no convincing evidence that glyphosate exposure is linked with the development of multiple myeloma (Sorahan 2015).

The studies relied on by the Working Group for animal carcinogenicity comprised two dietary studies in male and female mice, five dietary studies in male and female rats, as well as one drinking-water study of a glyphosate-based formulation in male and female rats.

In mice, one dietary study reported in summary form by the US EPA calculated a positive trend in the incidence of renal tubule carcinoma and renal tubule adenoma/carcinoma combined in male, but not female mice (IARC 2015). A second dietary study reported by the JMPR (2006) in mice observed a significant positive trend in the incidence of haemangiosarcoma incidence in male, but not female mice (IARC 2015). However, haemangiosarcomas were only observed at the highest dose tested in male mice (4/50; 8%). In females, haemangiosarcomas were reported at the lowest (2/50, 4%) and highest (1/50, 2%) doses tested.

Three dietary studies in rats evaluated by the JMPR found no significant increase in tumour incidence in any tissue (JMPR 2006). Of the remaining two studies (evaluated by the US EPA), one reported an increase in the incidence of pancreatic cell adenoma in male rats only; however, no statistically significant dose-response was evident and there was no progression to carcinomas (IARC 2015). In the final study, a significant increase in the incidence of

pancreatic islet cell adenoma and hepatocellular adenoma in males and thyroid C-cell adenoma in females was reported. However, again, there was no statistically significant dose-related trend in the incidence of pancreatic islet cell adenomas and no progression to carcinoma for any tumour type (IARC 2015). No significant increase in tumour incidence was observed following administration of a glyphosate formulation (13.85% solution, purity of glyphosate not reported) to rats in drinking water.

The Working Group concluded that there was strong evidence that glyphosate and glyphosate-based formulations are genotoxic and, along with the main metabolite, AMPA can act to induce oxidative stress. Two studies investigated genotoxicity following exposure of community residents to glyphosate-based formulations, reporting chromosomal damage (micronucleus formation) in blood (Paz-y-Miño et al. 2007) and significant increases in DNA damage (DNA strand breaks) (Bolognesi et al. 2009) four or two months following spraying, respectively. Other studies assessing the effects of either glyphosate or glyphosate-based formulations in human cells *in vitro* produced varied results (IARC 2015). The majority of the studies relied on by the Working Group that assessed genotoxicity in human cells *in vitro* reported DNA damage (DNA strand breaks), which can also be indicative of cytotoxicity and not just genotoxicity. Two studies were relied on by IARC as evidence of chromosomal damage in human lymphocytes *in vitro*. Both studies reported that glyphosate did not produce chromosomal damage without metabolic activation (Manas et al. 2009; Mladinic et al. 2009b). One study reported micronucleus formation following metabolic activation at the highest concentration tested only, but no concentration-related increase in micronucleus formation was evident (Mladinic et al. 2009b). Similarly, experiments utilising glyphosate or glyphosate-based formulations conducted in animals, both *in vivo* and *in vitro* produced varied results (IARC 2015). As for mammalian cells *in vitro*, many of the non-human mammalian genotoxicity studies utilised a DNA damage endpoint, which may be associated with cytotoxicity, rather than genotoxicity. One study assessing mutations in mouse uterine cells reported negative results. Four of the nine studies that assessed chromosomal damage (micronucleus formation) in mouse bone marrow cells produced negative results. Of the remaining five studies that reported positive results, three tested a single dose only, one reported a positive effect at the highest dose tested only and one reported a positive effect at the lowest dose tested only (IARC 2015). No chromosomal aberrations were reported following exposure to glyphosate (single ip dose) (Li & Long 1988) or a single oral dose of a glyphosate-based formulation in mouse bone marrow cells (Dimitrov et al. 2006); however, a single ip dose of a glyphosate-based formulation increased chromosomal aberration in a dose- and time-dependent manner (Prasad et al. 2009).

The Working Group concluded that there was weak evidence that glyphosate may affect the immune system and that glyphosate or glyphosate-based formulations induce receptor-mediated effects, such as aromatase activity. The Working Group also concluded that glyphosate-based formulations may affect cell proliferation or death, the latter via apoptosis; however, glyphosate alone either had no effect or had a weaker effect than the formulated products (JMPR 2006; IARC 2015).

4.2 Assessment of the IARC Monograph

The assessment of the IARC Monograph was undertaken by the Department of Health (OCS). The APVMA requested that OCS conduct a preliminary scoping review of the IARC Monograph to ascertain the relevance of the carcinogenicity classification of glyphosate and any implications that this may have to the registration of glyphosate and glyphosate-based formulations in Australia. In particular, the APVMA requested that OCS identify any relevant data not previously evaluated by Australia. This constituted Tier 1 of the OCS assessment (Supporting document 1).

Tier 2 of the OCS scoping assessment involved a detailed review of any studies that had been reviewed by IARC as part of its assessment of glyphosate and were identified by OCS as requiring further review during the Tier 1 assessment (Supporting document 2).

Previous OCS epidemiological review in 2005

An association between reported glyphosate use and an increased risk of NHL was reviewed by the OCS in 2005 (unpublished). Therefore, the OCS did not assess the epidemiological studies described in the IARC monograph published prior to 2005 and recommended that the APVMA rely on international assessments for any additional epidemiological information relating to glyphosate exposure. The OCS' unpublished 2005 assessment of epidemiological information relating to glyphosate exposure is summarised below.

The first report of an association of glyphosate exposure with NHL was from a case-control study conducted in Sweden; however, this estimate was based on only four exposed cases and three controls (Hardell & Eriksson 1999). A pooled analysis of this initial study with a study of hairy cell leukaemia (a rare subtype of NHL) suggested a relationship between glyphosate exposure and an increased risk of the disease (unadjusted analysis with an OR of 3 and 95% CI 1.1–8.5) (Hardell et al. 2002). A more extensive study across a large region of Canada found an increased risk of NHL associated with glyphosate use of 2 days or more per year, based on 23 exposed cases and 31 controls (OR = 2.1; 95% CI 1.2–3.7) (McDuffie et al. 2001). In a pooled analysis of case-control studies conducted in the US, De Roos et al. (2003) reported an association between glyphosate exposure and increased NHL risk in men after adjustment for other commonly used pesticides, based on 36 exposed cases and 61 controls (OR = 2.1; 95% CI 1.2–4.0).

By contrast, in another cohort study, De Roos et al. (2005) reported that glyphosate exposure was not associated with increased NHL risk in men after adjustment for other commonly used pesticides, based on 92 exposed cases. One plausible explanation for this conflicting result is that all previous studies had a lower number of exposed cases and were retrospective in design, and thereby susceptible to recall bias of exposure reporting. As information on exposures is obtained by questionnaires and interview of farmers or their next-of-kin, often years after the event, the quality of data on pesticide use obtained by recall is questionable (Blair et al. 2002). Indeed, recall bias is particularly problematic for widely used products such as Roundup and the potential for recall bias and for misclassification of pesticides were acknowledged as one of the limitations in all such studies. On the other hand, the study by De Roos et al. (2005) reported a higher number of exposed cases and was prospective in design, which should have largely eliminated the possibility of recall bias. On this basis and also based on the toxicity profile of glyphosate derived from animal studies, it is unlikely that exposure to this chemical is associated with an increased risk of NHL.

This is further supported by a recent epidemiological report showing that NHL incidence decreased between 1991–2000 in Sweden, Finland, Denmark and the US (Hardell & Eriksson 2003), a period in which glyphosate use increased very significantly. It is of interest to note that decreased NHL incidence during this period in Sweden also coincides with a decline in the prevalence of human immunodeficiency virus (HIV), which has been shown to be a risk factor for NHL (Pluda et al. 1993).

Tier 1 assessment of the IARC glyphosate monograph

Tier 1 assessment outcomes

REFERENCE LIST AND KEY STUDY REVIEW

The OCS examined the reference list from the IARC Monograph 112, which included 264 published papers. Publicly available papers were sourced and designated as either:

- relevant for the carcinogenicity classification for humans and requiring further analysis (Tier 2, Part 1)
  - studies previously reviewed by the EU or
  - studies not previously reviewed by the OCS or EU and
    - studies that used glyphosate technical
    - studies that investigated carcinogenicity, genotoxicity or oxidative stress
    - Studies that used relevant test animal models or cell lines, eg mouse, rat, human lymphocytes
- relevance for the carcinogenicity classification for humans unclear and to be determined internationally (the APVMA will rely on international assessment of these studies)
  - studies previously reviewed by the EU or
  - studies not previously reviewed by the OCS or EU and
    - studies that used a formulation of glyphosate
    - studies that were unclear as to the formulation or combination of active constituents used
    - Studies that do not fit the criteria for the other designations
- not relevant to the classification and excluded
  - studies previously reviewed by the OCS
  - studies undertaken using animal models or cell lines not relevant for assessing human toxicity; eg fish, frogs, bovine
  - studies investigating endpoints not relevant to a carcinogenicity classification; eg endocrine disruption, reproduction, immune function, neurotoxicity
  - environmental fate and residue studies
  - determination of glyphosate in air, soil, water or in vivo
  - market/industry summary publications
  - case studies regarding glyphosate poisoning
  - occupational exposure or biomonitoring studies.

Following analysis of the study abstracts, 174 references were excluded from requiring further review. The majority of these papers were excluded because the study utilised non-conventional species or methodology for evaluating human toxicity (eg fish). A total of 19 references were considered relevant to the carcinogenicity classification of glyphosate, requiring further in-depth revision. Of these 19 studies, 9 had been previously reviewed by the EU in

2013 and 10 had not previously been reviewed by either the OCS or the EU. The remaining 71 references were considered to require further review to determine their relevance to the carcinogenicity classification. Of these 71 references, 19 had been previously reviewed by the EU in 2013, five were referenced as US EPA papers (not referenced by the EU) and 47 had not been previously reviewed by either the OCS or EU. These studies will be assessed in detail by the JMPR in 2016.

RECOMMENDATIONS

Based on the Tier 1 assessment, the OCS recommended an evaluation of the studies listed in Table 4 (Appendix A) and an evaluation of the EU position for the key studies listed in Table 5 (Appendix B). This review constituted Tier 2 of the OCS scoping assessment of glyphosate. The studies referenced in the IARC Monograph that were not recommended for evaluation by the OCS are listed in Appendix C (Table 6).

The OCS noted that parallel reviews of the IARC Monograph were being planned or were in progress by independent expert international bodies (eg JMPR). Therefore, the OCS recommended that rather than undertaking a full review in isolation, the APVMA make use of this international assessment. This approach is consistent with the APVMA's policy on the use of international assessments.

Tier 2 assessment of the IARC glyphosate monograph

The Tier 2 assessment involved:

- Evaluation of 19 studies relevant to the carcinogenicity classification of glyphosate (Table 4, Appendix A). Of these, 16 were either considered or critically appraised by EFSA (2015).
  - 12 genotoxicity studies
  - 5 oxidative stress studies
  - 1 epidemiology study
  - 1 classification review report.

The Tier 2 assessment did not include a detailed review of the epidemiological studies or studies that evaluated the possible carcinogenicity of glyphosate-based formulations, as a number of international reviews of the IARC Monograph will be undertaken concurrently with the OCS assessment. A total of 47 studies that were not reviewed by the EU Renewal Assessment Report (RAR) and 19 studies that were reviewed by the EU RAR (Table 5, Appendix B) were not reviewed by the OCS in the Tier 2 assessment of glyphosate because their relevance to the carcinogenicity classification for humans was unclear. The APVMA will rely on international assessments of these studies.

Animal carcinogenicity studies

The OCS evaluated one published study that reviewed animal carcinogenicity studies to support regulatory requirements (Greim et al. 2015). The review paper included nine rat and five mouse studies in a weight-of-evidence assessment of the carcinogenicity of glyphosate that included a review of absorption, distribution, metabolism and excretion (ADME), acute toxicity, genotoxicity, epidemiology and animal chronic toxicity studies.

The authors refer to an article that qualitatively analysed the outcomes from seven cohort studies and 14 case-control studies that examined an association between glyphosate and cancers. No consistent pattern of positive statistical associations between total cancer or site-specific cancer in adults or children exposed to glyphosate was evident (Mink et al. 2012). All studies cited by Mink et al. (2012) were referenced in the IARC Monograph and five (Nordstrom et al. 1998; Hardell & Eriksson 1999; McDuffie et al. 2001; Hardell et al. 2002; De Roos et al. 2005) were included in a previous assessment of glyphosate by the OCS in 2005, which concluded that glyphosate is not mutagenic or carcinogenic and it is unlikely that exposure to glyphosate is associated with an increased risk of NHL. Of the remaining studies cited by Mink et al. (2012), four (Brown et al. 1990; Cantor et al. 1992; Carreon et al. 2005; Andreotti et al. 2009) were considered during the Tier 1 assessment as not appropriate for review because glyphosate was not referred to in the abstract and the remaining 12 were identified as requiring additional assessment in order to determine their relevance to the assessment. Therefore, a detailed appraisal of this paper was not conducted by the OCS as a part of the Tier 2 assessment.

Several one year toxicity studies in animals were reviewed by Greim et al. (2015) but not discussed in detail, as they were not designed to detect neoplasms. However, studies conducted in both rats and dogs indicated low toxicity of glyphosate following repeated daily exposure.

Greim et al. (2015) evaluated five chronic toxicity/carcinogenicity studies (conducted over a minimum duration of 18 months) in mice, four of which were considered reliable and were performed according to GLP following OECD testing guidelines (OECD TGs). In four of those studies, spontaneous tumours were observed at all doses. As no dose-response was observed, these were not considered to be treatment-related. One study observed evidence for an increase in the incidence of malignant melanomas at the highest dose tested; however, this tumour is known to be a common spontaneous tumour in the strain of mouse tested. Another study reported increased incidence of bronchio-aveolar adenocarcinoma and malignant lymphoma at the highest dose tested only; however, these were only observed in males and are known to be a common age-related neoplasm in the strain of mouse tested.

Greim et al. (2015) evaluated nine chronic toxicity/carcinogenicity (24 to 29 months) studies in rats submitted by industry, seven of which were conducted according to principles of GLP. Of the two non-GLP studies, one was conducted prior to the introduction of GLP. Some of the studies reported spontaneous and/or age-related neoplasms that did not exhibit a dose-response relationship and were therefore not considered treatment-related. In some cases, the tumours observed were known to be common age-related tumours in the particular strain of rat used. In addition, some studies reported the development of benign tumours that did not exhibit a dose-response relationship and did not progress to malignant neoplasms. Other studies reported no increase in tumour incidence following glyphosate exposure.

Greim et al. (2015) combined the results from the animal studies with results from human carcinogenicity epidemiology conclusions reported by Mink et al. (2012)[3] and concluded that glyphosate is not carcinogenic. They noted that while some studies reported an increase in a specific neoplasm at high dose, the pooled data did not identify any consistent pattern of neoplasm development or dose-response relationship. Therefore, the authors

[3] Mink et al (2012) concluded that there was no consistent evidence of an association between exposure to glyphosate and cancer in humans.

concluded that the observed effects were not consistent or reproducible and were not treatment related. The OCS agreed with the conclusion that the evidence indicates that glyphosate is not carcinogenic in animals.

Genotoxicity

The OCS appraised 11 studies and one review paper that assessed the genotoxicity of glyphosate.

DNA DAMAGE

Of these studies, six assessed genotoxicity via the comet assay (or single cell gel electrophoresis; SCGE) *in vitro*, using lymphocytes (Mladinic et al. 2009a; Mladinic et al. 2009b; Alvarez-Moya et al. 2014), HepG2 cells (liver carcinoma cells) (Gasnier et al. 2009), Hep-2 cells (epithelial carcinoma cells derived from a cervical cancer) (Manas et al. 2009), GM38 cells (diploid fibroblast cells) or HT1080 cells (fibrocarcinoma cells) (Monroy et al. 2005). All of these studies were considered by the EFSA RAR (2015). As previously described, DNA damage observed using sister chromatid exchange (SCE) or the comet assay is regarded as an indirect measure of genotoxicity and positive results using these endpoints may reflect induction of cytotoxicity, rather than genotoxicity, as DNA damage does not directly measure heritable events or effects that are closely associated with heritable events (Kier & Kirkland 2013).

The OECD TG 489 (2014) for comet assays specifies that exposure to the test substance should occur *in vivo* and cells subsequently isolated and analysed. In contrast, the study by Alvarez-Moya et al. (2014) exposed isolated human peripheral blood lymphocytes directly in vitro to the test substance. Therefore, it is difficult to compare these results with other studies as the exposed cells are likely to be more sensitive to direct exposure. Given this and other limitations in study design and reporting (including a lack of data relating to cytotoxicity), the OCS concluded that the genotoxic effects of glyphosate could not be determined from this study and that it was not reliable for regulatory purposes. Mladinic et al. (2009a) concluded that glyphosate technical is not genotoxic and does not cause oxidative stress at levels relevant to human exposure, and recommended further research utilising a larger sample population. The EFSA RAR (2015) noted that, while the study was a non-GLP, non-guideline study, it met broad scientific principles to determine genotoxicity; however, the positive results obtained at the highest dose tested may reflect cytotoxicity, rather than a true chromosome effect that would indicate genotoxicity. The OCS agreed with the assessment and concluded that the study demonstrated that glyphosate is not genotoxic and does not cause oxidative stress at concentrations relevant to human exposure, but that the results are only reliable as supporting evidence for regulatory purposes. In another study, the same research group concluded that glyphosate technical did not damage DNA at levels of expected human exposure (Mladinic et al. 2009b). However, the EFSA RAR noted a number of critical deficiencies in the study design and reporting (eg the study was not conducted according to GLP or international guidelines, and the proposed mechanism of genotoxicity is not relevant to human exposure levels). The OCS agreed with the conclusion of EFSA that the study is not suitable for regulatory (ie risk assessment) purposes.

Manas et al. (2009) concluded that glyphosate technical was genotoxic (as evidenced by DNA damage) in human Hep-2 cells between 3.00 and 7.50 mM (higher concentrations were cytotoxic) and Gasnier et al. (2009) concluded that exposure to a glyphosate-based formulation was genotoxic to human liver carcinoma (HepG2) cells. However, the study design and level of reporting detail of both studies was criticised by both EFSA and the OCS for a number of reasons. The positive results obtained by Gasnier et al. (2009) were observed only at exceedingly high concentrations that were above the limit dose limit, the potential for cytotoxicity due to membrane damage from surfactants is well known and was not controlled for, the results cannot be fully attributed to glyphosate technical

but may be related to the surfactants, no statistical analysis was performed, variation within the datasets were not reported (despite each experiment being conducted in triplicate) and there was an inadequate level of data reporting. Therefore, both EFSA and the OCS concluded that neither of the studies were suitable for regulatory purposes.

Monroy et al. (2005) reported a concentration-related increase in DNA migration in both normal human GM38 cells and human fibrosarcoma (HT1080) cells, which were statistically significant between 4 and 6.5 mM glyphosate and 4.75 and 6.5 mM glyphosate, respectively. At the highest dose (6.5 mM), DNA damage was approximately 5% and 30% for GM38 and HT1080 cells, respectively. Therefore, the authors concluded that glyphosate induces single-strand DNA breaks in mammalian cells. However, the EFSA RAR and OCS both identified a number of deficiencies in study design and reporting. The EFSA RAR (2015) suggested that the positive results seen may be secondary to cytotoxicity and the concentrations used may be at the threshold for cytotoxicity. When the cytotoxicity and genotoxicity results are combined, significant cytotoxicity (as defined by the authors as < 80% cell viability) was evident at 4.75 mM in HT1080 cells, at which genotoxicity results should therefore no longer be considered reliable. No negative control DNA migration results were reported for the HT1080 cells.
At concentrations at and below 5.5 mM, there was no significant change in the length of migration. The percentage of DNA that was not damaged remained higher than the 'DNA damage' scores combined until 5.5 mM.
In combination, these results suggest a lack of genotoxic potential at non-cytotoxic concentrations (4.75 mM).
For the GM38 cells, 80% of cells were viable at the highest concentration (6.5 mM) tested. Therefore, the data that reported significant DNA migration for the GM38 cells appear reliable. The DNA migration data support the DNA morphology data, with the percentage of cells with no DNA damage only remaining higher than the DNA damage combined up to 4 mM. Therefore, the OCS concluded that the results for HT1080 cells were not reliable for regulatory purposes and that the results for GM38 cells are reliable as supporting evidence only, due to a number of study design and reporting limitations.

One study utilised the SCE assay to assess genotoxicity in human lymphocytes, which was also considered by EFSA. Bolognesi et al. (1997) reported both glyphosate technical (purity not specified) and a glyphosate-based formulation induced a concentration-related increase in SCEs from 1 to 6 mg/mL and 0.1 to 0.33 mg/mL, respectively, and that a larger effect occurred with the formulated product than glyphosate technical. However, the EFSA and OCS identified a number of critical deficiencies in study design and reporting, including deviations from OECD guidelines: the experiment was conducted only in the absence of an exogenous source of metabolic activation; positive controls were not included and therefore the validity of the test system was not confirmed; only pooled data were provided (precluding assessment of the influence of inter-individual variation) and only two subjects were included, which does not allow a meaningful statistical analysis). Therefore, both EFSA and OCS concluded that the study was not reliable for regulatory purposes.

Bolognesi et al. (1997) investigated the potential for glyphosate (300 mg/kg) or Roundup® (900 mg/kg) to induce single-strand DNA breaks following ip administration, using the alkaline elution assay. EFSA concluded that the positive results of this assay may be secondary to cytotoxicity, as the doses of glyphosate were close to or in excess of the ip LD50 of glyphosate in mice. The OCS agreed with this assessment and concluded that the results of the alkaline elution assay are not reliable for regulatory purposes.

GENE MUTATION AND CHROMOSOMAL DAMAGE

Chromosomal effects, such as induction of chromosomal aberrations or micronuclei in cultured mammalian cells are considered direct measures of genotoxicity. Five studies assessed genotoxicity of glyphosate using the *in vivo*

micronucleus assay in various strains of mice, while one utilised the *in vitro* micronucleus assay in human lymphocytes. Significantly increased micronuclei, nuclear buds and nucleoplasmic bridges were reported following glyphosate treatment in the presence of metabolic activation at the highest concentration tested (580 µg/mL glyphosate) in human lymphocytes, but not at concentrations likely to be encountered by humans (Mladinic et al. 2009b). However, both the OCS and EFSA concluded that this study was not suitable for regulatory purposes: positive and negative control results were virtually indistinguishable, negative control data were not reported and despite the authors' claims that the concentrations of glyphosate tested correspond to acceptable safety levels based on evaluated *in vitro* endpoints, these findings need to be validated *in vivo*.

Four of the five reported *in vivo* micronucleus assays (Rank et al. 1993; Bolognesi et al. 1997; Manas et al. 2009; Prasad et al. 2009) utilised the ip administration route, which is not considered relevant for human exposure. Only one *in vivo* study (Chan & Mahler 1992) utilised a more appropriate dietary exposure model. A small but significant increase in micronucleus frequency was observed in male CD-1 mice, following ip exposure (two injections at a 24 hourly interval) to either 300 mg/kg glyphosate technical or 450 mg/kg Roundup® (equivalent of approximately 135 mg/kg glyphosate) (Bolognesi et al. 1997). However, positive controls were not used to validate the assay and the assay was not conducted according to international test guidelines, which specify that a minimum of three doses of the test substance be assessed in order to determine whether a dose-response relationship exists. In Balb-C mice, a significant increase in micronucleated erythrocytes was observed at high concentrations of glyphosate only (400 mg/kg) (Manas et al. 2009); however, this study was criticised by both EFSA and the OCS for major deviations from international test guidelines. In particular, erythrocytes (instead of immature, polychromatic erythrocytes) were scored for micronuclei and it did not appear that scoring was blinded. In Swiss albino mice, it was reported that glyphosate induced a significant dose- and time-dependent increase in bone marrow micronucleated polychromatic erythrocytes (Prasad et al. 2009). Again, this study was criticised by both EFSA and the OCS as the use of dimethyl sulphoxide (DMSO) as a solvent is highly unusual (glyphosate is soluble in water) and ip administration of DMSO has been shown to enhance the toxicity of glyphosate-based formulations. In contrast, no increase in micronucleus frequency was observed following dietary exposure in B6C3F1 mice (Chan & Mahler 1992) or ip exposure in NMRI-Bom mice (Rank et al. 1993). Positive control animals were treated for only 4 weeks (compared with 13 weeks for treated animals) in the dietary exposure study (Chan & Mahler 1992); therefore, the OCS concluded that the results were reliable only as supportive data for regulatory purposes. The other studies were not considered reliable for regulatory purposes, due to the limitations described above.

By applying centromere probes, Mladinic et al. (2009a) analysed micronuclei and nuclear instability in human lymphocytes exposed to glyphosate, with and without metabolic activation. The authors reported a significant increase in the proportion of micronuclei that contained centromeres only at the highest concentration of glyphosate tested (580 µg/mL) with metabolic activation, which the authors suggested could indicate aneugenic activity that is exhibited only above a threshold concentration. The number of early apoptotic and necrotic cells were significantly increased at 580 µg/mL, with and without metabolic activation. The authors concluded that glyphosate technical is not genotoxic at concentrations relevant to human exposure. The OCS agreed with the authors' conclusion and with EFSA's conclusion that the results are reliable as supporting evidence for regulatory purposes. Furthermore, the OCS agrees with EFSA that the positive results obtained at the highest dose tested indicated a possible threshold aneugenic effect associated with cytotoxicity, rather than a DNA-reactive clastogenic effect.

Three studies assessed genotoxicity using chromosome aberration studies in bone marrow cells obtained from Swiss albino mice (Prasad et al. 2009), SD mice (Li & Long 1988) and human lymphocytes (Manas et al. 2009).

The authors reported that glyphosate induced a significant dose- and time-dependent increase in aberrant cells compared with untreated cells in Swiss albino mouse bone marrow cells (Prasad et al. 2009), but not SD mice (Li & Long 1988) or human lymphocytes even at very high concentrations (up to 6 mM glyphosate) (Manas et al. 2009). However, as described above, the study by Prasad et al. (2009) was not considered suitable for regulatory purposes, as DMSO was used as the solvent (instead of water) and the glyphosate/DMSO solution was administered via ip injection. Li & Long (1988) deviated from international guidelines by testing only one concentration of glyphosate, examining only 50 cells per animal for aberrations and by administering glyphosate by ip injection. Manas et al. (2009) deviated from international guidelines by scoring 100 cells per treatment (instead of 200 cells), not reporting replicate data and not concurrently assessing cytotoxicity.

In addition to the chromosome aberration assay, Li & Long (1988) utilised a variety of other methods to assess genotoxicity, including prokaryotic genotoxicity tests (*Salmonella*/histidine plate incorporation reversion assay, *E. coli* WP2 reverse mutation assay, *B. subtilis* Rec-assay) and *in vitro* mammalian genotoxicity tests (Chinese hamster ovary hypoxanthine-guanine phosphoribosyl transferase or CHO-HGPRT gene mutation assay, unscheduled DNA synthesis). No positive responses were reported in any of the tests performed and the authors concluded that glyphosate is not genotoxic. Despite some deviations from international guidelines (only one positive control used and duplicate (rather than triplicate) plating was used in the *Salmonella*/histidine reversion assay and *E. coli* WP2 reverse mutation assay), the OCS and EFSA both concluded that the negative genotoxicity results of Li & Long (1988) were acceptable for regulatory purposes. Rank et al. (1993) also utilised the *Salmonella* plate incorporation reversion assay to assess genotoxicity; however, only Roundup® was tested and only two of the five recommended bacterial strains were used. The authors reported a weak mutagenic effect at 360 µg/plate in one strain (TA98) without metabolic activation and at 720 µg/plate in another strain (TA100) with metabolic activation. However, EFSA concluded that a reliable assessment was not possible due to marked cytotoxicity at and above 360 µg/plate and the lack of a concentration-response relationship. The OCS agreed with EFSA's assessment and concluded that the results were not reliable for regulatory purposes.

Overall, the OCS concluded that the weight-of-evidence indicates that glyphosate is not genotoxic in mammals at concentrations relevant to human exposure.

Oxidative stress

Overall, seven studies assessed the potential for glyphosate to induce oxidative stress. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and their elimination. ROS are important for cell signalling and cycling and are normally physiologically-controlled to prevent cell damage.

Three studies assessed ROS production in response to in vitro treatment of human HepG2 cells with glyphosate (Chaufan et al. 2014), keratinocytes (HaCaT) (Elie-Caille et al. 2010) and erythrocytes (Kwiatkowska et al. 2014). In human HepG2 cells, a significant increase in ROS formation was observed in cells treated with a glyphosate-based formulation (140% of control), but not glyphosate technical or the glyphosate metabolite, AMPA (Chaufan et al. 2014). However, the OCS concluded that this study was of limited regulatory value, as: the product assessed is not registered for use in Australia; the concentration of glyphosate in the formulated product was unclear and cytotoxicity was higher than that observed for glyphosate technical. In addition, the LC_{50} for the formulation was used in the experiments on ROS formation, while the LC_{20} was used for the other treatments. In human keratinocytes, hydrogen peroxide (H_2O_2) was increased in cells treated with 50 mM glyphosate for 30 minutes (Elie-Caille et al. 2010). The concentrations of glyphosate used in this study were very high (between 10 and 70 mM). As the experiments were performed at the IC_{50}, cell responses due to osmotic stress rather than

glyphosate toxicity cannot be excluded. Furthermore, the EFSA RAR noted that the conclusion that treatment with glyphosate (50 mM) for 30 minutes resulted in overproduction of H_2O_2 was based on a qualitatively thicker and more intense fluorescent area in the cell cytosol, but no quantitative measurement was obtained. The OCS added that light microscopy images of the cells were not included. In human erythrocytes, significantly increased ROS production was observed following exposure to glyphosate, its metabolites and impurities at concentrations up to 5 mM (Kwiatkowska et al. 2014). However, the results were provided graphically without actual data, hence it is not possible to independently evaluate these results. Furthermore, no positive controls were tested, therefore the validity of the assays cannot be ascertained.

Chaufan et al. (2014) also investigated the enzymatic (catalase, CAT; glutathione-S-transferase, GST; superoxide dismutase, SOD) and non-enzymatic antioxidant activity (glutathione equivalents, GSH) in human HepG2 cells *in vitro* following exposure to either glyphosate, AMPA or a glyphosate-based formulation. Exposure to glyphosate did not increase the activity of any of the antioxidants evaluated. Exposure to a glyphosate-based formulation caused a significant increase in SOD and GSH activity, while exposure to AMPA also caused a significant increase in GSH. Tyrosine kinases are also important mediators of the cell signalling processes that are involved in various process such as cell proliferation and apoptosis, and have also been implicated in the development of cancer (Paul & Mukhopadhyay 2004). Chaufan et al. (2014) reported that exposure to the glyphosate-based formulation, but not glyphosate or AMPA increased tyrosine nitration compared with controls.

Overall, the OCS concluded that there was limited evidence for an increase in ROS production following exposure to glyphosate, its metabolites or impurities, or a glyphosate-based formulation in *in vitro* cell culture studies using high concentrations of the test substances; however, the weight-of-evidence indicates that exposure to glyphosate at concentrations relevant to human exposure is unlikely to result in increased ROS production in humans.

Caspases participate in the programmed cell death pathway. Some apoptotic cells display caspase 3/7 activity, in contrast to necrotic cells. Two studies investigated caspase activity *in vivo* in male Wistar rats, following ip administration of glyphosate (alone or in combination with other pesticides) (Astiz et al. 2009) and *in vitro* in human HepG2 cells (Chaufan et al. 2014). In rats, ip administration of glyphosate alone did not induce caspase 3 activity in liver or brain (Astiz et al. 2009). However, the sample size was small (n=4), the study was only conducted in males and the administration route (ip injection) is not directly relevant to human exposure scenarios. In human HepG2 cells, caspase 3/7 activity was indirectly measured in cell lysates. Caspase 3/7 activity was significantly increased by a glyphosate-based formulation, but not glyphosate technical. The OCS concluded that oxidative stress and apoptosis may be plausible mechanisms of action for the *in vitro* cytotoxicity of the glyphosate-based formulation; however, the concentrations of treatments were not specified, limiting the value of the study. Furthermore, the product assessed by Chaufan et al. (2014) is not registered for use in Australia, the concentration of glyphosate in the formulated product was unclear and the concentrations of treatments were not specified.

Calpains have also been implicated in apoptosis. In addition to investigating caspase activity, Astiz et al. (2009) also investigated calpain activity *in vivo* in male Wistar rats following exposure to glyphosate alone and in combination with dimethoate and/or zineb. In the liver, milli-calpain activity was not affected by glyphosate alone. In the brain, milli-calpain activity was significantly reduced in both the substantia nigra and cerebral cortex by glyphosate alone. The authors reported that similar data were obtained for μ-calpain activity, but the data were not presented in the publication. While the results presented by Astiz et al. (2009) were considered by IARC to be supportive of an oxidative stress mechanism of action for carcinogenicity by glyphosate, EFSA and the OCS both concluded that the results reported in brain tissue were not biologically plausible for humans, due to the

blood-brain barrier and rapid elimination of glyphosate via urine. Therefore, the OCS concluded that there was no reliable evidence that glyphosate exposure would be likely to increase caspase or calpain activity in humans following exposure via relevant administration routes.

Bolognesi et al. (1997) investigated oxidative stress in Swiss CD-1 male mice (n=3 per dose) following administration of either 300 mg/kg glyphosate technical or 900 mg/kg of Roundup® (~270 mg/kg glyphosate) via ip injection. Glyphosate technical increased 8-OhdG (8-hydroxy-2'-deoxyguanosine)—a marker of oxidative stress—in the liver 24 hours post-treatment, but did not stimulate a response in the kidney. In contrast, Roundup® increased 8-OhdG in the kidney at 8 and 24 hours post treatment, but did not induce a response in the liver. However, as no positive controls were used the validity of the assay cannot be confirmed.

Oxidative potential and impact on DNA was measured in human lymphocytes using Ferric-inducing ability of plasma (FRAP), thiobarbituric acid reactive substances (TBARS) and the human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) modified comet assay (Mladinic et al. 2009a). The authors reported significantly increased oxidative activity (increased frequency of micronuclei, nuclear buds, nucleoplasmic bridges, total antioxidant capacity (FRAP) and lipid peroxidation (TBARS)) at 580 µg/mL glyphosate. These effects were generally greater in the presence of an exogenous source of metabolic activation. However, no clear concentration-dependent effect was observed for any parameter. The number of early apoptotic and necrotic cells were significantly increased at 580 µg/mL, with and without metabolic activation. The authors concluded that glyphosate does not cause oxidative stress at concentrations relevant to human exposure. The OCS agreed with the conclusion by EFSA that as the study was not conducted according to international guidelines, it can only be used as supporting evidence for regulatory purposes and agrees with the authors' conclusions that the lack of a clear dose-response relationship coupled with positive effects only being apparent at the highest concentration of glyphosate tested indicate that glyphosate is not likely to cause oxidative stress at levels relevant to human exposure.

Three studies assessed various aspects of cell morphology and structural integrity *in vitro* in various human cell lines: HepG2 cells (Chaufan et al. 2014), keratinocyte HaCaT cells (Elie-Caille et al. 2010) and erythrocytes (Kwiatkowska et al. 2014). Human HepG2 cells treated with a glyphosate-based formulation exhibited a higher percentage of condensed and fragmented nuclei (23.5%) indicative of apoptotic cell death compared with negative controls, but positive control data was not provided (Chaufan et al. 2014). Although the OCS concluded that the glyphosate-based formulation was likely to be a stimulator of apoptosis, based on the changes in nuclear morphology and increased caspase 3/7 activity *in vitro*, they also concluded that this study was considered to be of limited regulatory value, for the reasons stated above. In human keratinocytes, exposure to glyphosate resulted in shrunken, elongated cells with significantly affected cell adhesion potential, indicative of apoptosis (Elie-Caille et al. 2010). However, the authors cautioned that the cell line used (HaCaT) exhibits possible distinct functional deficiencies compared with normal human keratinocytes and the results cannot be directly extrapolated to *in vivo* keratinocyte behaviour. Furthermore, a two-fold reduction in cell numbers was also observed. The OCS concluded that it was not possible, based on the information provided in the paper, to determine whether glyphosate induced structural cellular changes or whether sub-confluent cells may inherently develop abnormal morphology due to the reduction in cell numbers. In human erythrocytes, glyphosate exposure did not induce morphological changes (Kwiatkowska et al. 2014). In addition, Astiz et al. (2009) investigated the integrity of the inner and outer mitochondrial membranes and peroxidation of mitochondrial membrane lipids *in vivo* in male Wistar rats, again in both liver and brain cells. As the OCS concluded that the results in brain tissue were not biologically plausible in humans, only the results obtained from liver tissue are considered here. Glyphosate alone did not significantly reduce either inner or outer mitochondrial membrane potential and did not affect mitochondrial cardiolipin content in liver (Astiz et al. 2009). Nevertheless, the OCS and EFSA concluded that the study by Astiz et al. (2009) was

not reliable for regulatory purposes. Although the OCS concluded that there was limited evidence that a glyphosate-based formulation may be capable of stimulating apoptosis, there was not sufficient reliable information indicating that glyphosate is involved in apoptosis in humans, at realistic exposure concentrations and administration routes.

Overall, the OCS concluded that no definitive conclusions could be drawn on the ability of glyphosate products and their associated impurities to induce oxidative stress, as there is limited reliable information available regarding the involvement of an oxidative stress mechanism for inducing cytotoxicity.

4.3 Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

The JMPR is an expert scientific body that was established in 1963 and meets annually to scientifically evaluate pesticide residues in food. The JMPR provides expert scientific advice to the Codex Alimentarius Commission and its specialist committee on pesticide residues, the Codex Committee on Pesticide Residues. The Codex Alimentarius develops international food standards and guidelines, with the aim of protecting consumer health, ensuring fair trade practices and promoting coordination of all food standards work undertaken by government and non-government organisations.

There are two expert panels that meet in parallel (hence the term 'Joint Meeting'), the Toxicology Panel (the WHO's Core Assessment Group on pesticides), and the Residues Panel (Organised by the Food and Agricultural Organisation of the United Nations). The Toxicology Panel of the JMPR is responsible for evaluating the adverse effects of pesticides on human health (including carcinogenicity) and establishing health-based guidance values which in turn are important for establishing MRLs used in international trade. The Residues Panel are responsible for evaluating the dietary risks from residues present on food commodities and for setting MRLs. The JMPR is also at the forefront of developing new risk assessment methodologies for pesticides and setting international scientific policy on the interpretation of toxicological studies. Participation in the JMPR is not representational but based on expertise in toxicology and pesticide risk assessment.

The relationship between the WHO, JMPR and IARC

The WHO was established in 1948 to direct and coordinate international health within the UN's system. The IARC is the specialised cancer agency of the WHO, but has its own Governing Council and Scientific Council. While the JMPR also works under the banner of the WHO, its role is to conduct risk assessments for pesticide residues in food, which includes the potential for pesticide residues in food to adversely affect human health in many ways, not just the potential to cause cancer.

The IARC classifies various chemicals, substances and situations in terms of their carcinogenic hazard, which indicates that some level of exposure could increase the risk to cancer. On the basis of this hazard identification and classification process, the JMPR may determine that it is necessary to evaluate or re-evaluate the safety of residues of that chemical in food, following its use in agriculture. Therefore, the two processes are complementary: the IARC determines whether a chemical may potentially cause cancer, while the JMPR determines whether it is likely humans will develop cancer following exposure to realistic residues of that chemical in food.

Assessment process

The process used by JMPR to assess potential risks associated with pesticide residues in food is described in detail in the International Programme on Chemical Safety (IPCS) Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food, which is a joint publication of the FAO and WHO. The IPCS has developed definitions of hazard and risk, which are adopted by JMPR for its risk analyses (IPCS 2009):

- hazard—inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent
- risk—the probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

Therefore, a risk assessment of food chemicals involves characterising the potential hazards associated with the chemical, as well as the potential risks to life and health resulting from exposure to those chemicals present in food over a specified period of time. This means that as well as looking at the potential for a chemical to cause harm, a risk assessment also considers the probability of that harm occurring as a result of realistic exposure scenarios. A risk assessment conducted by JMPR comprises four steps (IPCS 2009):

- Hazard identification—identification of the type and nature of adverse effects that a chemical is able to cause, taking into account the nature of the health hazard and the circumstances under which a hazard may be expressed.
- Hazard characterisation—assessment of the relationship between the administered dose of or exposure to a chemical and the incidence of the observed adverse health effect, including where possible, a dose-response relationship between increasing dose and health hazard incidence.
- Exposure assessment—evaluation of the exposure of for example, a human to a chemical and its derivatives, taking into account the occurrence and concentrations of the chemical in the diet, consumption patterns of foods containing the chemical, the likelihood of people consuming large amounts of those foods and the likelihood of high concentrations of the chemical being present in those foods. There are usually a range of intake or exposure estimates, which may be broken down by subgroups of the population.
- Risk characterisation—the information from the hazard characterisation and exposure assessment is integrated into suitable advice for risk-based decision making, by providing estimates of the potential risk to human health under various exposure scenarios, as well as the nature, relevance and magnitude of these risks.

The information generated from a risk characterisation may be either qualitative or quantitative, as defined by IPCS (2009) (Table 3). Any areas of uncertainty that result from gaps in the scientific evidence or any information on particularly susceptible subpopulations (eg young children, people with predisposing physiological conditions or people using the chemical as part of their occupation etc.) should be clearly outlined in the risk characterisation.

Table 3: Examples of qualitative and quantitative information outlined by the International Programme on Chemical Safety

Qualitative information	Quantitative information
Statements or evidence that demonstrates an absence	A comparison of dietary exposures with health-based

of toxicity even at high exposure levels	guidance values
Statements or evidence of safety in the context of specified uses	Estimates of risks at different levels of dietary exposure
Recommendations to avoid, minimise or reduce exposure	Risks at minimum and maximum dietary intakes
	Margins of exposure

The IPCS describes the general principles of toxicological study design, which should include compliance with GLP and adherence to internationally recognised organisations that provide guidance for standards of design and conduct of toxicological studies, such as the OECD. The IPCS outlines acceptable study design principles for determining absorption, distribution, metabolism and excretion, as well as general systemic toxicity, acute toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, food allergies/hypersensitivities and effects on the gastrointestinal tract and gut flora. There are also specific guidelines on designing and conducting studies in humans.

The IPCS goes on to provide guidance on the conduct of dose-response assessments, stating that where there is 'sufficient plausibility' for the presence of a cause-effect relationship, dose-response data are essential (IPCS 2009). Guidance is provided for setting health-based guidance values for substances present in food and drinking water, which are used to quantitate the range of acute or chronic oral exposure that presents no appreciable health risk. The ADI is generally set on the basis of the lowest NOAEL in the most sensitive species; however, a benchmark dose may also be used to determine the ADI. Where appropriate, an ARfD is also developed. Generally, a 100-fold uncertainty factor is used to convert the NOAEL obtained from a study using experimental animals into a health-based guidance value in humans; however, additional uncertainty factors may also be applied in certain circumstances (described by IPCS) (IPCS 2009). The default 100-fold uncertainty factor represents two 10-fold factors that allow for:

- differences between average responses in animals and average responses in humans
- variability in responses between average humans and highly sensitive humans.

Guidance is provided by IPCS on how to perform and interpret acute and chronic dietary exposure assessments for chemicals present in food. This assessment combines data about food consumption patterns with data about the concentration of chemicals in food to provide a dietary exposure estimate, which can be compared with the relevant health-based guidance value available for that chemical. The assessment should include the general population, as well as more vulnerable groups, or people expected to have different exposures from the general public, such as infants, pregnant women etc (IPCS 2009).

Pesticide residue data is evaluated by JMPR according to the IPCS guidelines, using data generated from pesticide use that was conducted according to Good Agricultural Practice, which stipulates that effective pest control be achieved while leaving the smallest residue amount practicable. National legislation stipules MRLs, which are the maximum concentrations of pesticide (or veterinary drug) residues permitted in or on a food.

Importantly, the IPCS provides guidance on how to perform a risk characterisation as a part of the risk assessment process, which integrates the information obtained during the hazard characterisation process and the exposure assessment to provide advice to risk managers (IPCS 2009).

Assessment of glyphosate

Glyphosate has been assessed by JMPR in 2003, 2006 and most recently, in 2011. Following the IARC decision in March 2015 to reclassify glyphosate as 'probably carcinogenic to humans' and noting that new data may have been generated since the JMPR's most previous assessment of glyphosate in 2011, the WHO established an ad hoc expert taskforce to evaluate the available data relating to glyphosate and report its findings to JMPR. The task force completed its assessment of the IARC monograph in September 2015 and recommended that JMPR conduct a full re-evaluation of glyphosate, as the IARC assessment included a number of peer reviewed scientific publications that had not been available during the JMPR's 2011 assessment (WHO 2015).

In October 2015, the WHO issued a data call for a number of substances, including glyphosate. This evaluation of glyphosate was discussed at an extraordinary meeting of the JMPR at WHO headquarters in Geneva, Switzerland on 9 to 13 May 2016. The Meeting summary report was published online in May 2016.

The summary report contained a description of how the Meeting evaluated genotoxicity and epidemiological evidence for the active constituent glyphosate, glyphosate-based formulated products and metabolites (JMPR 2016). The Meeting evaluated a large number of genotoxicity studies that were identified via various means: direct submission to JMPR, searches of publicly available literature, requests to the IARC Monographs Secretariat, or requests to industry groups. The Meeting also searched databases for any relevant articles published after the studies cited in the IARC Monograph, using defined search terms. These studies were either unpublished studies that had been submitted by a sponsor to support an application for registration (the majority of which adhered to internationally accepted guidelines) or peer-reviewed studies published in the scientific literature. The studies were separated into categories that reflected their phylogenetic relevance and the significance of the genetic end-point measured: human biomonitoring studies, *in vivo* mammalian studies, *in vitro* mammalian cell culture models, *in vitro* bacterial models, phylogenetically distant organisms, metabolites *in vivo* and finally, metabolites *in vitro*. Overall, mammalian *in vivo* studies were given more weight than *in vitro* cell culture studies or studies using phylogenetically distant organisms, and studies of gene mutations and chromosomal alterations were given more weight than studies measuring less serious or transient types of genotoxic damage. Studies that measured the effects of oral exposure were considered to be more relevant for determining dietary exposure. Human biomonitoring studies were most likely to be confounded by exposure to other pesticides or other limitations. An overall weight-of-evidence assessment approach was used to reach conclusions about the genotoxicity of glyphosate, based on an evaluation of the studies using the criteria described above as well as an assessment of the overall quality of each study.

The meeting used a pre-agreed evaluation process, as described in the JMPR (2016) Meeting summary, to:

- select glyphosate/cancer site combinations for inclusion in the evaluation
- screen papers for inclusion or exclusion in the evaluation
- evaluate the information for risk assessment.

Glyphosate/cancer site combinations were included if IARC identified positive associations from the evidence it assessed and all studies cited by IARC, published since the IARC assessment was completed or identified from reference lists of already identified papers were screened for inclusion in the evaluation. Papers were included if they were the most recent publication with the longest follow-up period for that glyphosate/cancer site combination and/or the most complete analysis of that glyphosate/cancer site combination with the largest sample size/number

of participants, providing that the exposure assessment was specific to glyphosate and quantitative (ie exposure was expressed on a ratio scale), and that the paper was relevant and could contribute to a quantitative risk assessment for that glyphosate/cancer site combination.

As described in the JMPR (2016) Meeting summary, for each paper that was included in the assessment:

- the quantitative exposure units were determined
- the magnitude of effect or uncertainty was described
- the quality of the study was reviewed
- the exposure assessment was described
- the manner in which exposure levels compared or translated to glyphosate residue levels or pathways was described.

As described in the JMPR (2016) Meeting summary, for each glyphosate/cancer site included in the assessment:

- the hazard from all studies contributing to the quantitative risk assessment was characterised
- the strength-of-evidence was summarised.

When evaluating the evidence for glyphosate/cancer site associations, the Meeting considered factors that would decrease the level of confidence in the body of evidence (including the risk of bias, unexplained inconsistencies and imprecision) as well as factors that would increase the level of confidence in the body of evidence (including a large magnitude of effect, dose-response and consistency) (JMPR 2016). When evaluating the information available for risk assessment and hazard characterisation, the Meeting evaluated the overall evidence for dose-response relationships, by comparing risk estimates with quantitative exposure measures (eg days of use per year) (JMPR 2016).

The Meeting considered prospective cohort studies to be a more powerful study design than case-control studies, as case-control studies are usually retrospective and are therefore more prone to recall and selection biases (JMPR 2016). The one large, prospective cohort study (the AHS cohort) found no evidence of a positive association between glyphosate exposure and NHL incidence. Various case-control studies reported varying results, with some reporting elevated risks (both significant and non-significant) and others not observing an association. The Meeting concluded that there was some evidence of a positive association between glyphosate exposure and the risk of NHL; however, the AHS—a large, high-quality prospective cohort study found no evidence of an association at any exposure level (JMPR 2016).

The Meeting identified nine carcinogenicity studies in mice, two of which were considered to be of insufficient quality for inclusion in the assessment (JMPR 2016). Equivocal evidence of lymphoma induction was apparent in 3/7 studies in male mice and 1/7 studies in female mice at high doses (5000–40 000 ppm or 814–4348 mg/kg bw/day). In contrast, higher doses (up to 50 000 ppm or 7470 mg/kg bw/day) in the remaining three studies did not cause an effect. In 4/7 studies, there was a trend for a marginal increase in induction of kidney adenomas in male mice at the highest dose tested; however, again, higher doses failed to illicit a response.

The Meeting identified 11 combined chronic toxicity and carcinogenicity studies in rats; however, one was considered inadequate for carcinogenicity assessment (short exposure duration of only 12 months) (JMPR 2016).

An increased incidence of various tumours (interstitial cell tumours of the testes, pancreatic islet cell adenoma, thyroid C-cell tumours, skin keratoma) was observed in 1/10 or (in one case) 2/10 studies. However, in all cases, higher doses used in other studies did not illicit a response. The Meeting also reported a lack of dose-response relationship for some tumour types. There was no evidence for spleen or kidney lymphoma induction in any of the studies. Therefore, the Meeting concluded that there was no reliable evidence for treatment-related tumours in rats at doses of up to 32 000 ppm (or 1750 mg/kg bw/day).

The Meeting concluded that glyphosate is not carcinogenic in rats, but was unable to exclude the possibility that glyphosate is carcinogenic in mice at very high doses (JMPR 2016).

The overall weight-of-evidence suggested that oral doses of up to 2000 mg/kg bw/day glyphosate (either alone or in a formulated product) are not associated with genotoxic effects in the majority of studies in mammals. In cell culture models and organisms that are phylogenetically different to humans, DNA damage and chromosomal effects have been observed following exposure to glyphosate. However, these effects have not been replicated in oral *in vivo* mammalian model studies. Therefore, the Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures (JMPR 2016).

The Meeting's overall conclusion relating to the carcinogenic potential of glyphosate was that, the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity in mammals following oral exposure, along with the epidemiological evidence from occupational exposure indicated that glyphosate is unlikely to pose a carcinogenic risk to humans via exposure from the diet (JMPR 2016).

The Meeting also concluded that there was no evidence from seven studies in rats that up to 30 000 ppm (or 1983 mg/kg bw/day) glyphosate resulted in reproductive toxicity. There was also no evidence for teratogenicity or developmental toxicity in rats (up to 3500 mg/kg bw/day; four studies) or rabbits (low-incidence fetal effects were observed in 3/7 studies at doses that exceeded maternal toxicity). There was no evidence of endocrine disruption, with a range of *in vitro* and *in vivo* assays demonstrating no interaction with oestrogen or androgen receptor pathways or thyroid pathways. There was no evidence of neurotoxicity in rats (up to 2000 mg/kg bw/day) or immunotoxicity in female mice (up to 500 ppm, or 1448 mg/kg bw/day) (JMPR 2016).

Finally, the Meeting concluded that the extent to which glyphosate adversely effects the microbiota of the human or mammalian GIT is unclear, as this is an emerging area of scientific research. However, the available information on minimum inhibitory concentration values suggest that it is unlikely that dietary glyphosate residues would be capable of adverse effects on normal GIT microbiota function (JMPR 2016).

The Meeting further concluded that the glyphosate metabolite, AMPA, is unlikely to be genotoxic following oral exposure in mammals and there was no evidence for embryo or fetal toxicity. Similarly, two other metabolites, *N*-Acetyl-glyphosate and *N*-Acetyl-AMPA are unlikely to be genotoxic in mammals (JMPR 2016).

4.4 European Food Safety Authority (EFSA)

Assessment process

The European Food Safety Authority requires scientific information that has adhered to OECD guidelines on toxicological testing of chemicals and the EU Test Method Regulation No. 440/2008, which stipulates in detail how the studies must be conducted. By European law, all required studies must be conducted according to the

principles of GLP. Scientific information that does not meet these standards but has been published in peer-reviewed journals are also included in the assessment.

When evaluating the carcinogenic effects of a chemical, the RMS delegated to conduct the assessment must follow the classification criteria outlined in EU Regulation (EC) No 1272/2008 on CLP criteria. The CLP criteria for establishing the level of evidence (eg sufficient, limited evidence etc.) for a carcinogenic effect are similar to those used by IARC; however, additional factors that influence the overall likelihood that a substance may be carcinogenic to humans must be taken into account. The emphasis placed on each individual factor is dependent on the amount and coherence of available evidence. Generally, more complete evidence is required to decrease the level of concern than is required to increase the level of concern. Some examples of factors to be taken into account include:

- tumour type and background incidence
- multi-site responses
- progression of lesions to malignancy
- reduced tumour latency
- whether responses are in single or both sexes
- whether responses are in single or multiple species
- structural similarity of the chemical to another substance for which there is good evidence of carcinogenicity
- routes of exposure
- comparison of absorption, distribution, metabolism and excretion between experimental animals and humans
- the possibility of a confounding effect of excessive toxicity at experimental doses
- mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression or mutagenicity.

Assessment of glyphosate

Glyphosate is registered for use throughout Europe and the UK and in 2010 was subjected to a re-assessment by the RMS, Germany, as mandated by the EC and coordinated by EFSA (See Section 2.3).

The BfR concluded that glyphosate was 'unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential' (EFSA 2015).

During the re-evaluation process, the BfR evaluated more than 150 new toxicology studies and re-assessed nearly 300 toxicological studies, as well as considering around 900 scientific publications and reviewing more than 200 in detail. The BfR concluded that the available data do not demonstrate that glyphosate exhibits carcinogenic or mutagenic properties or that it has adverse effects on fertility, reproduction or embryonal/fetal development in laboratory animals. The BfR concluded that there was convincing evidence that the toxicity associated with some glyphosate-containing products was attributable to co-formulants, such as tallowamines used as surfactants.

In July 2015, the BfR was commissioned to review the IARC monograph on the re-classification of glyphosate.

The BfR agreed with the conclusion that there is 'limited evidence in humans for the carcinogenicity of glyphosate' and its assessment of the epidemiological studies was comparable to that of the IARC Working Group. However, the BfR also noted that no consistent positive association between glyphosate exposure and the development of cancer was demonstrated and the most statistically highly-powered study detected no effect. The BfR further noted that it was not possible to differentiate between the effects of glyphosate and the co-formulants from the epidemiology studies discussed in the IACR monograph (Germany 2015).

The BfR disagreed with the conclusion by the IARC Working Group that there is 'sufficient evidence in animals for the carcinogenicity of glyphosate', which was based on a positive trend in the incidence of rare renal tumours, a positive trend for haemangiosarcoma in male mice and increased pancreatic islet-cell adenoma in male rats. The BfR assessed the studies relied on by the IARC Working Group and concluded that the weight-of-evidence suggests that there is no carcinogenic risk related to the use of glyphosate and that no hazard classification for carcinogenicity is warranted according to the CLP criteria (Germany 2015). Three studies conducted in mice reported a significant positive trend for renal tumours following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, the analysis by pair-wise comparisons did not demonstrate a significant difference between the groups and the incidences of tumours were within the historical control range (up to 6% for adenoma and carcinoma combined). Similarly, two studies conducted in mice reported a significant positive trend for haemangiosarcoma following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, analysis by pair-wise comparisons did not demonstrate a significant difference between the groups. Furthermore, the background incidence for haemangiosarcoma in male mice is up to 12%. Two of three studies conducted in mice reported a significant positive trend for malignant lymphoma following glyphosate exposure, when data were analysed using the Cochran-Armitage test for linear trend; however, the analysis by pair-wise comparisons did not demonstrate a significant difference between the groups in all three studies. Again, the incidences of malignant lymphoma were within the historical control range (up to 12%). The BfR determined that a significant difference to the incidence of pancreatic islet cell adenomas in rats occurred in the low dose group only, therefore was considered incidental (ie there was no dose-response effect). Therefore, the BfR concluded that the observed incidences of renal tumours, haemangiosarcoma and malignant lymphoma were spontaneous and not related to glyphosate exposure.

The BfR also disagreed with the IARC's conclusion that there 'is mechanistic evidence for genotoxicity, oxidative stress, inflammation, immunosuppression, receptor-mediated effects, and cell proliferation or death of glyphosate'. The BfR concluded that a weight-of-evidence assessment approach indicates that neither glyphosate nor AMPA induce mutations *in vivo* and no hazard classification for mutagenicity was warranted according to CLP criteria (Germany 2015). It further concluded that the mechanistic and other studies do not provide evidence for a carcinogenic mechanism. Consistently negative results were observed in *in vitro* bacterial assays and mammalian cell gene mutation assays and the majority (all of the GLP-compliant studies) of the *in vitro* chromosomal aberration tests and micronucleus tests were also negative. *In vitro* studies produced negative results for induction of DNA repair but positive results for induction of SCE and DNA strand breaks. *In vivo*, 14 somatic cell tests for induction of chromosomal aberrations or micronuclei were negative even at extremely high intraperitoneal doses and there was no evidence for mutagenic activity in germ cells. Two publications reported significant increases in micronuclei following ip administration; however, in both studies the dose tested was in the range of the ip LD_{50} of glyphosate in mice and one study was fundamentally flawed in design. Two publications reported induction of DNA strand breaks following exposure to very high ip doses or repeated oral doses, which were close to or exceeded the ip LD_{50} of glyphosate in mice; therefore, the observed positive results may be the result of secondary effects of cytotoxicity. However, the BfR noted that no firm conclusions can be drawn with regard to a need for classification according to the CLP criteria, regarding specific glyphosate-based formulations, for which there was some

evidence for *in vivo* mammalian chromosomal damage. The BfR recommended that further genotoxicity studies be conducted according to OECD test guidelines.

The BfR agreed with the IARC Working Group that glyphosate does not appear to exhibit endocrine disrupting properties (Germany 2015).

The BfR agreed with the IARC Working Group that there is some indication of induction of oxidative stress, based on *in vitro* studies using human cells and *in vivo* mammalian studies, particularly in blood plasma, liver, brain and kidney of rats; however, it was not indicative of genotoxic or carcinogenic activity in humans. Furthermore, the majority of this work was conducted using a glyphosate-based formulation rather than glyphosate alone. There was no indication of induction of oxidative stress by AMPA.

While the IARC Working Group concluded that there was 'weak evidence that glyphosate may affect the immune system, both the humoral and cellular response', the BfR concluded that the available data do not indicate that glyphosate or glyphosate formulations adversely affect the immune system (Germany 2015). However, it noted that the small number of available studies had methodological limitations and therefore no robust information was available to conclusively determine the possible immunomodulatory action of glyphosate. The BfR mostly agreed with the reporting of the studies relied on by IARC; however expanded on a number of points. For example, the IARC Working Group concluded that one study demonstrated 'pathological effects of glyphosate on the immune system' in rats (Chan & Mahler 1992). However, the only finding reported was a reduction in absolute/relative thymus weight in male rats at the highest dose of glyphosate tested. The BfR concluded that this reduction in thymus weight in male rats was likely related to non-specific toxicity, as evidenced by a lower weight gain and a lower final bodyweight (18%) in male rats, which was not observed in females.

4.5 The European Chemicals Agency (ECHA)

The ECHA is responsible for managing the harmonised classification (CLH) process for active constituent chemicals within plant protection products in the EU. The CLH is based solely on the hazardous properties (ie toxicity) of the chemical and does not take into account exposure; therefore, the CLH procedure conducted by ECHA is not a risk assessment. In that respect, the CLH procedure undertaken by ECHA is similar to the scope of the IARC assessment process.

As a part of the procedure for the renewal of the glyphosate registration in the EU, Germany submitted a proposal for CLH to ECHA. The ECHA launched a 45 day public consultation of the CLH proposal for glyphosate on 2 June 2016 (deadline for comment 18 July 2016). In addition to the existing CLH (eye irritation and aquatic toxicity), a new classification was proposed (ECHA 2016):

- STOT RE 2: May cause damage to organs through prolonged or repeated exposure.

This proposed classification was based solely on the results obtained from developmental studies conducted in rabbits (which appear to be the most sensitive laboratory animal species), where adverse effects (maternal toxicity; NOAEL = 50 mg/kg bw/day) occurred at doses lower than those occurring in the very large number of studies conducted in mice, rats and dogs over longer durations of exposure. Based on CLP hazard criteria, the NOAEL of 50 mg/kg bw/day is lower than the 28-day guidance value in rats (< 300 mg/kg bw/day) and therefore glyphosate technically qualifies for this statement.

The ECHA concluded that a weight-of-evidence approach indicated that glyphosate is not mutagenic and that no hazard classification for mutagenicity was warranted according to the CLP criteria (ECHA 2016). The ECHA considered that standard mutagenicity tests (eg cytogenetic tests or micronucleus assays) were more reliable and carried greater weight than 'indicator tests' (eg comet assays or DNA damage assessed via sister chromatid exchange or DNA strand breaks). Generally, these indicator tests are regarded as useful follow-up tests for confirmation of positive or equivocal standard *in vitro* test results.

Consistently negative results were obtained from *in vitro* bacterial assays and mammalian cell gene mutation assays. Guideline *in vitro* mammalian chromosome aberration tests and micronucleus tests also produced negative results. In contrast, positive results were reported in *in vitro* indicator tests for SCE and DNA strand breaks. Negative results were reported from 11 *in vivo* micronucleus tests or cytogenetic studies in somatic cells that followed international guidelines, while one study reported a weak positive effect in female mice receiving a very high (likely cytotoxic) dose. Inconsistent results were obtained in a number of published studies that did not adhere to international guidelines and generally tested low doses via the ip route. As for *in vitro* studies, positive results for DNA damage (eg strand breaks) were observed in a number of published indicator tests following high ip or repeated oral (via drinking water) administration, while a study assessing unscheduled DNA synthesis produced negative results. There was no evidence of mutagenic activity in germ cells of mice and rats following oral doses of up to 2000 mg/kg bw.

The ECHA concluded that a weight-of-evidence assessment of epidemiological data and data from long-term studies in both rats and mice indicate that no hazard classification for carcinogenicity was warranted for glyphosate according to the CLP criteria (ECHA 2016). In the discussion relating to carcinogenicity, the ECHA addressed the differing assessments of the available information by IARC and EFSA. The ECHA also noted that glyphosate differed from most other pesticides in that a number of comprehensive and high quality studies are available for nearly all toxicological endpoints.

A total of 5/8 long-term, guideline-compliant studies conducted in mice were considered by ECHA. The ECHA took into account the known very large variability of the incidence of spontaneous malignant lymphoma in both Swiss and CD-1 mice, the consistent lack of any dose-response relationship between tumour incidence and glyphosate exposure and the excessively high concentrations that elicited increased incidences of tumours in some studies and concluded that, overall, there was inconsistent evidence for the occurrence of malignant lymphoma, renal tumours and haemangiosarcoma in males but not females.

The ECHA evaluated a total of 7/11 studies conducted in rats, the majority of which (6/7) were guideline-compliant. The non-guideline study (Lankas 1981) was not considered suitable for regulatory purposes due to study design and reporting limitations. The ECHA took into consideration the consistent lack of statistical significance using pairwise analyses, the consistent lack of any dose-response relationships and the lack of reproducibility across multiple studies and concluded that there was no evidence for an association between glyphosate exposure and pancreatic islet cell adenomas, hepatocellular adenomas, C-cell thyroid adenomas or interstitial testicular tumours.

The ECHA also assessed human data on the potential carcinogenicity of glyphosate noting that the value of this data had limitations for regulatory assessments, as it was exclusively derived from epidemiological studies. Firstly, it is difficult to distinguish between the effects of the active constituent and co-formulants, because humans are never exposed to the active constituent alone. As the co-formulants are not only contained in glyphosate-based products, but are also contained within other formulated products, an assessment of the entire formulated product is not indicative of the safety of the active constituent or glyphosate-based products specifically. Secondly, humans

are exposed to a great number of environmental chemicals, making it difficult to attribute health effects to one specific chemical.

The ECHA described the results of the AHS study that analysed data from approximately 57 000 pesticide applicators. Analysis of this data did not identify an association between glyphosate and various forms of cancer, including leukaemia, melanoma, all lymphohaematopoietic cancers, NHL, or cancer of the lung, prostate, breast, colon, rectum, oral cavity, pancreas, kidney or bladder (De Roos et al. 2005; Blair & Freeman 2009). Some papers relied on by the IARC assessment reported positive associations between glyphosate exposure and NHL; however, this association was based on very small sample populations with low numbers of exposed subjects, relied on reported use (and was therefore susceptible to recall bias) by either primary or secondary (eg relatives) sources and was not statistically significant in one study (Nordstrom et al. 1998; Hardell & Eriksson 1999; McDuffie et al. 2001; De Roos et al. 2003; Hardell & Eriksson 2003; Eriksson et al. 2008). In contrast, the ECHA also described 18 papers that did not identify a risk between glyphosate exposure and various specific cancer types (Alavanja & Bonner 2012): prostate cancer (Alavanja et al. 2003; Band et al. 2011; Koutros et al. 2011), stomach and oesophageal adenocarcinomas (Lee et al. 2004), gliomas (Carreon et al. 2005), breast cancer (Engel et al. 2005; El-Zaemey et al. 2013), childhood cancer (following parental exposure) (Flower et al. 2004), pancreatic cancer (Andreotti et al. 2009), monoclonal gammopathy (Landgren et al. 2009), Hodgkin's lymphoma (Karunanayake et al. 2012), multiple myeloma (Pahwa et al. 2012; Kachuri et al. 2013), NHL (Schinasi & Leon 2014), lymphomas in general (including B cell lymphoma) (Cocco et al. 2013) or soft tissue sarcoma (Pahwa et al. 2011).

The ECHA concluded that, while epidemiological data is of limited value for detecting the carcinogenic potential of a pesticide, the data do not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type and no hazard classification for carcinogenicity is warranted for glyphosate according the CLP criteria (ECHA 2016).

Following the public consultation, any received comments will be provided to the Committee for Risk Assessment (RAC), which will form an opinion on the hazard classes that were open for consultation only. For glyphosate, these include: all health hazards except respiratory sensitisation and aspiration hazard (carcinogenicity, germ cell mutagenicity and reproductive toxicity) and all environmental hazards except ozone layer hazards. In addition, ECHA may request further clarification and contact some of those who commented to discuss specific issues. From there, any opinion of the CLH proposal must be adopted by RAC within 18 months from the receipt of that proposal by ECHA and the 'background document', which contains the CLH report with RAC evaluations inserted will be published on the ECHA website. The ECHA will then forward the RAC opinion to the EC, which will determine whether the CLH is appropriate.

4.6 Health Canada

In 2010, Health Canada's PMRA commenced a re-evaluation of glyphosate in collaboration with the US EPA's re-evaluation of glyphosate. In April 2015, the PMRA published its Proposed Re-evaluation Decision (PRVD2015-01) for glyphosate, as discussed above in Section 2.2. In conducting re-evaluations of registered products, the PMRA utilises data from holders of product registrations, as well as published scientific reports, information from other regulatory agencies and any other information considered relevant to the evaluation. The PMRA evaluation of the available scientific information concluded that there were no unacceptable risks to human health or the

environment as a result of using glyphosate according to the proposed label directions and no additional data were requested.

The re-evaluation report describes how the potential risks to human health are assessed, which is similar to the method employed by the APVMA. The PMRA re-evaluation of glyphosate determined that adverse effects observed in animals occurred at doses more than 100 times higher than levels to which humans are normally exposed when using glyphosate according to label directions. The re-evaluation reported that glyphosate has low acute oral, dermal and inhalational toxicity, does not irritate the skin or cause allergic skin reactions in laboratory animals; however, it was a severe eye irritant.

The PMRA determined that acute dietary exposure represented between 12% and 45% of the ARfD for all of the population subgroups. The chronic dietary exposure estimate for the general population represented 30% of the ADI, with a range of 20% to 70% of the ADI for the various population subgroups. As a result, the PMRA concluded that acute and chronic dietary risks were not of concern when glyphosate is used according to the label directions.

The re-evaluation also assessed residential handler exposure from mixing, loading and applying glyphosate product to residential lawns and turf (primarily dermal) as well as incidental oral exposure of children playing in treated areas. Bystander exposure was estimated for scenarios where people enter non-cropland areas, such as parks or hiking areas that had recently been treated with glyphosate. For all of these assessments, assessed either alone or in combination with background chronic dietary exposure (discussed above), no evidence of health risk was determined. Similarly, the risk estimates associated with mixing, loading and applying glyphosate in an agricultural scenario or re-entering treated agricultural sites did not demonstrate any health risks, based on the current directions for use and agricultural use patterns.

The PMRA re-evaluation report addressed the IARC conclusions, emphasising that a hazard classification is not a health risk assessment. They also stressed that the level of human exposure is the factor that determines the risk and that this was not taken into account in the IARC classification of glyphosate. The PMRA considered the epidemiological information included in the IARC assessment and concluded that the majority lacked adequate characterisation of glyphosate exposure, which limited their suitability for assessing the hazard of glyphosate.

The PMRA concluded that the available *in vitro* and *in vivo* tests demonstrated that glyphosate is not genotoxic in rats or mice and that glyphosate is not carcinogenic in rats. While there was some evidence for a marginal increase in the incidence of ovarian tumours in mice, no dose-response was evident and the increased incidence was only observed at the highest tested doses and historical control data were not available. Therefore, the PMRA concluded that these results were of low concern for human health risk assessment.

Overall, the PMRA concluded that the weight-of-evidence obtained from both acute and chronic animal toxicity studies, genotoxicity assays and epidemiology studies indicates that glyphosate is unlikely to pose a human cancer risk.

4.7 New Zealand Environmental Protection Authority

The New Zealand Environmental Protection Authority commissioned a review of the evidence relating to the carcinogenicity of glyphosate. The scope of the review covered the basis on which the IARC Working Group classified glyphosate as a probable human carcinogen, which involved reviewing the quality of the evidence for

carcinogenicity in humans and animal models, as well as the data used to support mechanistic arguments (Temple 2016).

The review concluded that a possible dose-response relationship in humans could not be evaluated, as the epidemiological evidence did not indicate whether any internal exposure was measured or, if there was, the extent of that exposure. The review also agreed with conclusions by WHO in 2006, which reported that weak, rarely statistically significant associations between glyphosate exposure and lymphopoietic cancers do not generally meet the criteria for determining causal relationships from epidemiology data.

The review discussed each epidemiological study relied on by the IARC Working Group in its assessment that there was 'limited evidence' for carcinogenicity in humans, following exposure to glyphosate, as well as a review conducted by Mink et al. (2012) and the assessment conducted by the BfR for EFSA. As with other assessments, the review placed more weight on the prospective AHS cohort study, which did not identify an association between glyphosate and NHL, or a number of other cancer types, even though exposure was higher than that presented in the case-control studies. The review highlighted the fact that only two of the case-control cohort studies cited by the IARC Working Group reported statistically significant increased ORs at the 95% confidence level (Temple 2016).

The review noted that a small, non-significant increased risk of multiple myeloma was identified in the AHS cohort (De Roos et al. 2005), but described in detail the reassessment of that data, which questioned that result (Temple 2016). This re-assessment argued that the reported elevated risk ratio (RR) for multiple myeloma were not relevant, as they resulted from a restricted data set that (most likely by chance) were not actually representative of the population (Sorahan 2015). That is, a number of cases of multiple myeloma in the group of pesticide applicators who had never used glyphosate were excluded from the original analysis because they did not have data about the use of alcohol, smoking etc. This resulted in a false impression of increased risk in ever users, compared with those who had never used glyphosate. The re-analysis resulted in a RR of 1.1 (Sorahan 2015), compared with the original estimated rate ratio of 2.6, reported by De Roos et al. (2005).

One Swedish case-control study reported an association between glyphosate exposure and cancer risk after more than 10 years of exposure (OR 2.26, 95% CI 1.16–4.4) using 29 exposed cases and 18 unexposed controls (Eriksson et al. 2008) and was considered by the IARC Working Group to be a large study. In contrast, Temple (2016) concluded that 29 cases and 18 controls could not be considered a large study and had limited power to detect an effect. The significant effect reported in this study was only significant using a univariate evaluation and there was the possibility that results could have been confounded by earlier exposure to MCPA (2-methyl-4-chlorophenoxyacetic acid), which is associated with an increased risk of NHL.

The review highlighted that the key studies cited in support of 'sufficient evidence' for carcinogenicity in experimental animals consisted of three studies in mice: a positive trend for increased renal tubule carcinoma in one oral study; a positive trend for increased incidence of haemangiosarcoma in one oral study; and tumour promotion in a skin study. The review also highlighted that the IARC Working Group used different statistical tests (trend analysis) to assess the data in those studies, compared with the original analysis (pairwise comparisons). In the original pairwise comparisons, none of the studies produced positive associations. The IARC Working Group also did not take into account historical incidence data or the presence of a viral infection which may have affected survival rates and lymphoma incidence in one study. In addition, a number of studies that have been used by other regulators (which did not support an association between glyphosate and carcinogenicity) were not considered by the IARC Working Group noting that this is consistent with the scope of IARC. The New Zealand

review concluded that the total database of long-term carcinogenicity bioassays were consistently negative and the positive findings reported by the IARC Working Group are not considered supportive of carcinogenicity by other reputable scientific bodies, therefore the overall weight-of-evidence does not indicate that glyphosate is carcinogenic (Temple 2016).

The review concluded that the studies relied on by the IARC Working Group as 'strong evidence' for genotoxicity and oxidative stress primarily utilised *in vitro* mammalian cell studies, in which mammalian cells are directly exposed to glyphosate (or a formulated product) at high concentrations that are not realistic to *in vivo* exposure in animals or humans. The review highlighted that all studies that followed internationally accepted guidelines produced negative results, while all positive associations were achieved in studies that used unvalidated test methods or species, glyphosate formulations, or high intraperitoneal doses that are widely considered inappropriate for assessing genotoxicity in humans (Temple 2016).

The overall conclusion of the review was that, based on a weight-of-evidence approach that considered the quality and reliability of the available data, glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification as either a carcinogen or a mutagen (Temple 2016).

4.8 Adverse Experience Reporting Program (AERP)

The AERP is a post-registration program that assesses reports of adverse experiences associated with the use of agricultural and veterinary products, when the product has been used according to the approved label instructions.

Between 1996 and 2013, a total of four AERs relating to human safety were submitted to the AERP. All were classified as 'possible' or 'probable' by the AERP. Of the four AERs, one related to skin irritation while the remaining three were reports of eye irritation.

5 ASSESSMENT OUTCOMES

In the Tier 1 assessment, the OCS examined the reference list from the IARC Monograph 112 for glyphosate, which included 264 publisher papers. Following analysis of the study abstracts, 174 references were excluded from requiring further review (Table 6), mostly because the study utilised non-conventional species or methodology for evaluating human toxicity (eg fish). A total of 19 references were considered relevant to the carcinogenicity classification of glyphosate, requiring further in-depth revision (Table 4). The remaining 71 references were considered to require further review to determine their relevance to the carcinogenicity classification (Table 5). The APVMA will rely on international assessments of these papers.

The OCS concluded that, based on the results of the critical appraisal and the limited number of studies reviewed by the OCS in the Tier 2 assessment, there did not appear to be any additional information to indicate that glyphosate poses a carcinogenic risk to humans, on the basis of the following:

- a carcinogenic mechanism of action via genotoxicity or oxidative stress is not evident
- the level of cytotoxicity associated with *in vitro* genotoxicity testing of glyphosate was significant, limiting the ability of *in vitro* tests to determine the genotoxicity potential of glyphosate.

The OCS noted that there is some evidence that *in vitro*, glyphosate-based formulated products are more toxic to cells than glyphosate; however, this effect has not been confirmed *in vivo*. Furthermore, many of the studies exhibited significant methodological limitations, reducing the usefulness of the data.

No definitive conclusions could be drawn on the ability of glyphosate-based formulations to induce oxidative stress as there is limited information regarding the involvement of an oxidative stress mechanism for inducing cytotoxicity.

The OCS concluded that glyphosate was unlikely to pose a carcinogenic or genotoxic risk to humans.

The APVMA evaluated a number of recent assessments of glyphosate conducted by international organisations and regulatory agencies (JMPR, EFSA, ECHA, Health Canada and the NZ Environmental Protection Authority), which considered the publicly available data that was considered in the IARC monograph, as well as other published and unpublished data using a weight-of-evidence approach.

The APVMA agreed with the international assessments of the available epidemiological data that, while epidemiological data is of limited value for detecting carcinogenic potential of a pesticide, the weight-of-evidence does not provide convincing evidence for an association between glyphosate exposure in humans and any cancer type, as there was no consistent pattern of statistical associations that would suggest a causal relationship between glyphosate exposure and the development of cancer in adults or children (total or site-specific).

The APVMA agreed with the international assessments that the weight-of-evidence in experimental animals indicates that glyphosate does not pose a carcinogenic risk at realistic exposure levels, as no consistent dose-response relationship was evident in mice or rats and many of the reported tumours are common age-related tumours in rats and mice.

The APVMA agreed with the international assessments that glyphosate is not likely to be genotoxic, as well-designed *in vitro* tests consistently reported negative results. While some *in vitro* studies reported positive

results for, these were generally observed following very high intraperitoneal doses and most likely a secondary effect of cytotoxicity.

Between 1996 and 2013, a total of four ‘possible’ or probable’ AERs relating to human safety (skin or eye irritation) were submitted to the AERP. The APVMA is confident that the current safety and use directions included on approved labels for products containing glyphosate are sufficient to mitigate these known adverse effects.

6 PROPOSED REGULATORY POSITION

On the basis of the evaluation of the scientific information and assessments, the APVMA concludes that the scientific weight-of-evidence indicates that:

- exposure to glyphosate does not pose a carcinogenic risk to humans
- there is no scientific basis for revising the APVMA's satisfaction that glyphosate or products containing glyphosate:
  - would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
  - would not be likely to have an effect that is harmful to human beings
  - would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
  - would be effective according to criteria determined by the APVMA by legislative instrument, and
  - would not unduly prejudice trade or commerce between Australia and places outside Australia.
- **there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration**
- the APVMA will continue to maintain a close focus on any new assessment reports or studies that indicate that any of the above conclusions may need revising.

APPENDIX A – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 REQUIRING FURTHER REVIEW BY OCS (TIER 2, PART 1)

The studies referenced in the IARC monograph that the OCS recommended for review are presented below in Table 4. These studies were selected according to the criteria outlined in Section 0 to be assessed in Tier 2, Part 1 of the OCS evaluation to determine whether glyphosate should be placed under formal reconsideration.

Table 4: List of studies relevant to the carcinogenicity classification of glyphosate that require evaluation

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
Alvarez-Moya, C, Silva, MR, Valdez Ramírez, CV, Gallardo, DG, Sánchez, RL, Aguirre, AC, & Velasco, AF	2014	genotoxicity	glyphosate isopropylamine	human (lymphocyte cell line)	Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms. Genetics and molecular biology, 37(1), 105–10	Comet assay; glyphosate isopropylamine; human lymphocytes; positive results	http://www.scielo.br/scielo.php?pid=S1415-47572014000100016&script=sci_arttext
*Astiz, M, de Alaniz, MJ & Marra, CA	2009a	oxidative stress	glyphosate	rat (unknown strain)	Effect of pesticides on cell survival in liver and brain rat tissues. Ecotoxicology and environmental safety,72(7), 2025–32	Liver and brain rat cell survival; MOA for oxidative stress seen in previous study	http://www.sciencedirect.com/science/article/pii/S0147651309001018
*Bolognesi, C, Bonatti, S, Degan, P, Gallerani, E, Peluso, M, Rabboni, R, Roggieri, P & Abbondandolo, A	1997	genotoxicity	glyphosate and Roundup	swiss CD-1 mice; human (lymphocyte cell line)	Genotoxic activity of glyphosate and its technical formulation Roundup. Journal of Agricultural and food chemistry, 45(5), 1957–62	Uses roundup and glyphosate alone; positive results seen in both	http://pubs.acs.org/doi/abs/10.1021/jf9606518
Chan, P & Mahler, J	1992	genotoxicity	glyphosate	F344/N rats and B6C3F1	NTP technical report on the toxicity studies of Glyphosate (CAS No.	Effects in rats and mice; no mutagenicity in	http://europepmc.org/abstract/med/12209170

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
				mice	1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice. Toxicity report series, 16, 1-D3	salmonella; negative for LLNA	
*Chaufan, G, Coalova, I & Rios de Molina Mdel, C	2014	oxidative stress	glyphosate, AMPA and glyphosate formulation	human (HepG2 cell line)	Glyphosate Commercial Formulation Causes Cytotoxicity, Oxidative Effects, and Apoptosis on Human Cells Differences With its Active Ingredient. International journal of toxicology, 33(1), 29–38	Shows formulation increases ROS and has toxic effects not seen in glyphosate alone	http://ijt.sagepub.com/content/33/1/29.short
*Elie-Caille, C, Heu, C, Guyon, C & Nicod, L	2010	oxidative stress	glyphosate	human keratinocyte (HaCaT cell line)	Morphological damages of a glyphosate-treated human keratinocyte cell line revealed by a micro-to nanoscale microscopic investigation. Cell biology and toxicology, 26(4), 331–39	Shows the timeline of membrane damage and ROS production in human keratinocytes	http://www.ncbi.nlm.nih.gov/pubmed/20043237
*Gasnier, C, Dumont, C, Benachour, N, Clair, E, Chagnon, MC & Seralini, GE	2009	genotoxicity	glyphosate and glyphosate formulations	human (HepG2 cell line)	Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. Toxicology, 262(3), 184–91	Shows effects are dependent on formulation not glyphosate concentration	http://www.sciencedirect.com/science/article/pii/S0300483X09003047
*Gehin, A, Guillaume, YC, Millet, J, Guyon, C & Nicod, L	2005	oxidative stress	glyphosate and round-up	human keratinocyte (HaCaT cell line)	Vitamins C and E reverse effect of herbicide-induced toxicity on human epidermal cells HaCaT: a biochemometric approach. International	Shows effects are due to formulation; uses human keratinocyte cell	http://www.sciencedirect.com/science/article/pii/S0378517304005733

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
					journal of pharmaceutics,288(2), 219–26	line	
Greim, H, Saltmiras, D, Mostert, V & Strupp, C	2015	carcinogenicity/ epidemiology	glyphosate and glyphosate formulations	human, rat, mouse	Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Critical reviews in toxicology, 45(3), 185–208	Shows no carcinogenic effect	http://www.tandfonline.com/doi/abs/10.3109/10408444.2014.1003423#.Vf9hMvk0VcY
JMPR	2006	classification					http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf?ua=1
*Kier, LD & Kirkland, DJ	2013	genotoxicity	glyphosate and glyphosate formulations	in vitro and in vivo	Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Critical reviews in toxicology,43(4), 283–315	Review of genotoxicity tesing for glyphosate and formulations	http://www.ncbi.nlm.nih.gov/pubmed/23480780
*Kwiatkowska, M, Huras, B & Bukowska, B	2014	oxidative stress	glyphosate, glyphosate metabolites and glyphosate impurities	human (erythrocyte cell line)	The effect of metabolites and impurities of glyphosate on human erythrocytes (in vitro). Pesticide biochemistry and physiology, 109, 34–43	Uses human erythrocytes; shows that ROS and damage only occurs at levels seen in acute poisoning	http://www.sciencedirect.com/science/article/pii/S0048357514000200
*Li, AP & Long, TJ	1998	genotoxicity	glyphosate	in vitro and in vivo	An evaluation of the genotoxic potential of glyphosate. Toxicological Sciences, 10(3), 537–46	Multiple genotoxicity tests; shows no genotoxic	http://toxsci.oxfordjournals.org/content/10/3/537.short

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
						potential	
*Manas, F, Peralta, L, Raviolo, J, Ovando, HG, Weyers, A, Ugnia, L, Cid, MG, Larripa, I & Gorla, N	2009a	genotoxicity	glyphosate	human (Hep-2 cell line); mouse micronucleus	Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. Environmental Toxicology and Pharmacology, 28(1), 37–41	Shows positive genotoxicity results in Hep-2 cells and micronucleus mouse test at 400 mg/kg	http://www.sciencedirect.com/science/article/pii/S1382668909000258
*Mladinic, M, Berend, S, Vrdoljak, AL, Kopjar, N, Radic, B & Zeljezic, D	2009a	genotoxicity	glyphosate	human (lymphocyte cell line)	Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro. Environmental and molecular mutagenesis, 50(9), 800–7	Shows no clear dose dependent effect	http://onlinelibrary.wiley.com/doi/10.1002/em.20495/abstract
*Mladinic, M, Perkovic, P & Zeljezic, D	2009b	genotoxicity	glyphosate	human (lymphocyte cell line)	Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and carbofuran using cytome FISH assay. Toxicology letters, 189(2), 130–7	Cytome FISH assay; shows no hazardous effect on DNA at low concentrations	http://www.sciencedirect.com/science/article/pii/S0378427409002616
*Monroy, CM, Cortes, AC, Sicard, DM & de Restrepo, HG	2005	genotoxicity	glyphosate	human (GM38 and fibrosarcoma HT1080 cell lines)	Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate.Biomedica, 25 (3), 335–45	Suggests MOA not limited to plants	http://www.scielo.org.co/scielo.php?pid=S0120-41572005000300009&script=sci_arttext&tlng=pt
Prasad, S, Srivastava, S, Singh, M &	2009	genotoxicity	glyphosate	swiss albino mice	Clastogenic effects of glyphosate in bone marrow cells of Swiss albino mice. Journal of toxicology,	Shows positive clastogenic and cytotoxic effects in mouse bone	http://www.hindawi.com/journals/jt/2009/308985/abs/

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/publication details	Comments	Website
Shukla, Y					2009	marrow	
*Rank, J, Jensen, AG, Skov, B, Pedersen, LH & Jensen, K	1993	genotoxicity	glyphosate isopropylamine salt and Roundup	in vitro and in vivo	Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, Salmonella mutagenicity test, and Allium anaphase-telophase test. Mutation Research/Genetic Toxicology, 300(1), 29–36	Shows negative effects for glyphosate in three genotoxicity tests	http://www.sciencedirect.com/science/article/pii/0165121893901362

*Considered by EFSA (2015)

APPENDIX B – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 THAT REQUIRE FURTHER REVIEW TO DETERMINE RELEVANCE TO THE CARCINOGENICITY CLASSIFICATION

The studies that were referenced in the IARC monograph that the OCS concluded required further assessment to determine their relevance to the carcinogenicity classification of glyphosate are presented below in Table 5. These studies were selected according to the criteria outlined in Section 0. The APVMA will rely on international assessments of these studies to determine whether glyphosate should be placed under formal reconsideration.

Table 5: List of studies recommended by the OCS for further assessment to determine if relevant to carcinogenicity classification of glyphosate

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
*Alavanja, MC, Samanic, C, Dosemeci, M, Lubin, J, Tarone, R, Lynch, CF, Knott, C, Thomas, K, Hoppin, JA, Barker, J, Coble, J, Sandler, DP & Blair, A.	2003	Carcinogenicity/ epidemiology	unknown formulation	human	Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. American Journal of Epidemiology,157(9), 800–14	No direct reference to glyphosate in abstract, increased risk to 'other pesticides' only seen in subjects with a FHx of prostate cancer	http://aje.oxfordjournals.org/content/157/9/800.short
*Astiz, M, de Alaniz, MJ, & Marra, CA.	2009b	oxidative stress	glyphosate	rat	Antioxidant defense system in rats simultaneously intoxicated with agrochemicals. Environmental toxicology and pharmacology, 28(3), 465–73	Glyphosate administered alone and in combo with other a.i.'s; unclear if results are for combo; in vivo rat model	http://www.sciencedirect.com/science/article/pii/S1382668909001392
Astiz, M, Hurtado de Catalfo, GE., García, MN, Galletti, SM,	2013	oxidative stress	glyphosate	wistar rat	Pesticide-induced decrease in rat testicular steroidogenesis is differentially prevented by	Oxidative stress seen in testicular cells; investigates	http://www.sciencedirect.com/science/article/pii/S0147651313000389

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
Errecalde, AL, de Alaniz, MJ, & Marra, CA.					lipoate and tocopherol. Ecotoxicology and environmental safety, 91, 129–38	antioxidant treatment after administration; unclear if administered in combo	
Benachour, N, & Séralini, GE.	2009	MOA	Roundup	human (umbilical, embryonic, placental cell lines)	Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells.Chemical research in toxicology, 22(1), 97–105	Uses glyphosate formulations, investigates metabolites	http://pubs.acs.org/doi/abs/10.1021/tx800218n
Benachour, N, Sipahutar, H, Moslemi, S, Gasnier, C, Travert, C, & Séralini, GE.	2007	MOA	Roundup (bioforce)	human (embryonic and placental cell lines)	Time-and dose-dependent effects of roundup on human embryonic and placental cells. Archives of Environmental Contamination and Toxicology,53(1), 126–33	Uses glyphosate formulations, investigates toxicity and endocrine-disruption	http://link.springer.com/article/10.1007/s00244-006-0154-8
*Bolognesi, C, Carrasquilla, G, Volpi, S, Solomon, KR, & Marshall, EJP.	2009	genotoxicity/ epidemiology	glyphosate + cosmo-flux	human	Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate.Journal of Toxicology and Environmental Health, Part A, 72(15-16), 986–97	Columbian aerial spray program; uses formulation as exposure to glyphosate; measurement of binucleated lymphocytes with micronuclei as DNA damage	http://www.tandfonline.com/doi/abs/10.1080/15287390902929741#.Ve0iNfk0VcY
Brewster, DW, Warren, J, & Hopkjns, WE.	1991	metabolism	glyphosate	SD rat	Metabolism of glyphosate in Sprague-Dawley rats: tissue distribution, identification, and	Tissue distribution study, shows no persistence in	http://toxsci.oxfordjournals.org/content/17/1/43.short

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
					quantitation of glyphosate-derived materials following a single oral dose.Toxicological Sciences, 17(1), 43–51	body after single oral dose	
Brown, LM, Burmeister, LF, Everett, GD, & Blair, A.	1993	carcinogenicity/epidemiology	unknown formulation	human	Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes & Control, 4(2), 153–56	No direct reference to glyphosate or roundup; shows little evidence of association between pesticides and multiple myeloma	http://link.springer.com/article/10.1007/BF00053156
Cattani, D, Cavalli, VLDLO, Rieg, CEH, Domingues, JT, Dal-Cim, T, Tasca, CI, & Zamoner, A.	2014	oxidative stress	Roundup	rat	Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: Involvement of glutamate excitotoxicity. Toxicology, 320, 34–45	Uses formulation; neurotoxic effects on rat hippocampus	http://www.sciencedirect.com/science/article/pii/S0300483X14000493
Çavuşoğlu, K, Yapar, K, Oruç, E, & Yalçın, E.	2011	oxidative stress	Roundup	SA mouse	Protective effect of Ginkgo biloba L. leaf extract against glyphosate toxicity in Swiss albino mice. Journal of medicinal food, 14(10), 1263–72	Uses formulation; ip to mice; studies the effect of Ginkgo against effects seen	http://online.liebertpub.com/doi/abs/10.1089/jmf.2010.0202
Chruscielska, K, Brzezinski, J, Kita, K, Kalhorn, D, Kita, I, Graffstein, B, & Korzeniowski, P.	2000	toxicity			Glyphosate. Evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy, 3	Chronic toxicity study review	

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
Coalova, I, de Molina, MDCR, & Chaufan, G.	2014	oxidative stress	atanor + impacto (adjuvant)	human (Hep-2 cell line)	Influence of the spray adjuvant on the toxicity effects of a glyphosate formulation. Toxicology in Vitro,28(7), 1306–11	Uses formulation and adjuvant on Hep-2 cell line; shows toxicity and ROS	http://www.sciencedirect.com/science/article/pii/S0887233314001295
Cocco, P, Satta, G, Dubois, S, Pili, C, Pilleri, M, Zucca, M, 't Mannetje AM, Becker, N, Benavente, Y, de Sanjose, S, Foretova, L, Staines, A, Maynadie, M, Nieters, A, Brennan, P, Miligi L, Enna, MG & Boffetta, P.	2012	carcinogenicity/epidemiology	unknown formulation	human	Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occupational and environmental medicine, oemed-2012	No direct reference to glyphosate; based on pesticide exposure determined via survey	http://oem.bmj.com/content/early/2012/10/31/oemed-2012-100845.short
Culbreth, ME, Harrill, JA, Freudenrich, TM, Mundy, WR, & Shafer, TJ.	2012	MOA	glyphosate	human; mouse	Comparison of chemical-induced changes in proliferation and apoptosis in human and mouse neuroprogenitor cells. Neurotoxicology, 33 (6), 1499–510	Apoptosis induced by glyphosate, neurodevelopmental study; uses human and mouse neural cells	http://www.sciencedirect.com/science/article/pii/S0161813X12001271
Dennis, LK, Lynch, CF, Sandler, DP, & Alavanja, MC.	2010	carcinogenicity/epidemiology	unknown formulation	human	Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environmental Health Perspectives, 118(6), 812–	Uses formulation; no results relating to glyphosate	http://www.ladep.es/ficheros/documentos/10(35).pdf

Author(s)	Year	Endpoint	Formulation type (if stated)	Species	Title/Publication details	Comments	weblink
					17		
*De Roos, A, Zahm, SH, Cantor, KP, Weisenburger, DD, Holmes, FF, Burmeister, LF, & Blair, A.	2003	carcinogenicity/epidemiology	unknown formulation	human	Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.Occupational and Environmental Medicine, 60(9), e11–e11	Uses formulation; shows positive trend with NHL	http://oem.bmj.com/content/60/9/e11.short
*Dimitrov, BD, Gadeva, PG, Benova, DK, & Bineva, MV.	2006	genotoxicity	Roundup	mouse (bone marrow)	Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems. Mutagenesis, 21 (6), 375–82	Comparative study using glyphosate formulation; negative results	http://mutage.oxfordjournals.org/content/21/6/375.short
*Engel, LS, Hill, DA, Hoppin, JA, Lubin, JH, Lynch, CF, Pierce, J, Samanic, C, Sandler, DP, Blair, A & Alavanja, MC.	2005	carcinogenicity/epidemiology	unknown formulation	human	Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. American Journal of Epidemiology,161(2), 121–35	Uses formulation; glyphosate not directly referenced in the abstract; no clear association with breast cancer	http://aje.oxfordjournals.org/content/161/2/121.short
*Eriksson, M, Hardell, L, Carlberg, M, & Åkerman, M.	2008	carcinogenicity/epidemiology	unknown formulation	human	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. International Journal of Cancer, 123(7), 1657–63	Uses formulation; results were not adjusted for multiple exposures; shows increased risk of NHL for glyphosate	http://onlinelibrary.wiley.com/doi/10.1002/ijc.23589/pdf

*Considered by EFSA (2015)

APPENDIX C – LIST OF KEY STUDIES REFERENCED IN THE IARC MONOGRAPH 112 REVIEWED BY THE EU IN 2013 THAT WERE NOT CONSIDERED BY THE OCS

Table 6 below lists the studies referenced in the IARC Monograph 112 for glyphosate that were not considered to require further evaluation by the OCS, as well as the reasons for exclusion.

Table 6: List of excluded studies based on criteria outlined in Section 4.2

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Abraxis	2005			Plate kit	No	No
Acquavella	2004			Biomonitoring	No	No
Akcha	2012	genotoxicity		Not a relevant human model – oyster	No	No
Alavanja	1996	N/A	Yes	Outline of agricultural health study	No	No
Alvarez-Moya	2011	genotoxicity		Not a relevant human model	No	No
Andreotti	2009	carcinogenicity		No direct reference to glyphosate	No	Yes
Aris	2011			Maternal and fetal exposure to pesticides associated with GM foods	No	No
Band	2011	carcinogenicity		No direct reference to glyphosate, refrence to malathion	No	Yes
Battaglin	2005			Transformation products in streams	No	No
Bernal	2010			Liquid chromatography	No	No
Blair	2011			Exposure misclassification in AHS	No	No
Blakley	1997	immune function		Not relevant to carcinogenicity classification	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Bonini	2006			Oxidation of dye in antioxidant activity assay	No	No
Borggaard	2008			Fate of glyphosate in soil	No	No
Botero-Coy	2013a			Improvements in analytical assay	No	No
Botero-Coy	2013b			Liquid chromatography of glyphosate in rice, maize, soybeans	No	No
Brown	1990	carcinogenicity	Yes	No reference to glyphosate	No	No
Bruch	2013			Leaching assessment programme	No	No
Cantor	1992	carcinogenicity	Yes	No direct reference to glyphosate, reference to malathion	No	No
Carreon	2005	carcinogenicity	Yes	No direct reference to glyphosate	No	Yes
Cattaneo	2011	oxidative stress		Not a relevant human model – fish	No	No
Cavalcante	2008	genotoxicity		Not a relevant human model – fish	No	No
Cavas	2007	genotoxicity		Not a relevant human model – goldfish	No	No
CCM International	2011			Outlook for Chinese glyphosate industry	No	No
Centre de Toxicologie du Quebec	1988			Exposure of forestry workers	No	No
Chandra	1994			Spontaneous renal lesions in strains of mice	No	No
Chang	2011			Fate of glyphosate in the environment	No	No
Chen	2012			DNA damage in cyanobacteria	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Chen	2013			Residues on fruit and vegetables	No	No
Chen	2009			Glyphosate poisoning in Taiwan	No	No
Clair	2012	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Clements	1997	genotoxicity		Not a relevant human model – tadpoles	No	No
ColomboPage News Desk	2014			Media—Sri Lanka lifts ban on sale of glyphosate	No	No
Connors	2004	genotoxicity		Not a relevant human model—mussel	No	No
Costa	2008	oxidative stress		Not a relevant human model—tadpoles	No	No
Curwin	2005			Pesticide contamination inside farm and non-farm homes	No	No
Curwin	2007			Uurinary pesticide conc.	No	No
de Castilhos	2013	genotoxicity		Not a relevant human model—fish	No	No
de Marco	1992			Soil breakdown of glyphosate	No	No
de Menezes	2011	oxidative stress		Not a relevant human model—fish	No	No
de Roos	2005a	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
de Roos	2005b	carcinogenicity	Yes	Response to criticism	No	No
de Souza	2013	genotoxicity		Not a relevant human model—fish, used roundup, concluded the results seen could have been due to excipients	No	No
Dill	2010			Glyphosate development, applications and properties	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
dos Santos	2014	genotoxicity		Not a relevant human model—clam, uses atrazine and glyphosate formulation	No	No
Duke	2009			Glyphosate resistant crops	No	No
EC	2002			EU report on glyphosate	No	No
EFSA	2008			Residues report	No	No
el-Gendy	1998	immune response		Not relevant to carcinogenicity classification, not a relevant human model—fish	No	No
US EPA	1980a	teratology		Not relevant to carcinogenicity endpoint	No	No
US EPA	1980b	teratology		Not relevant to carcinogenicity endpoint	No	No
US EPA	1992			Glyphosate in drinking water	No	No
US EPA	1997			Pesticides sales and usage	No	No
US EPA	2015			Tox database	No	No
US EPA	1991c			Peer review of glyphosate	No	No
US EPA	1993a			Glyphosate RED	No	No
US EPA	1993b			Glyphosate RED factsheet	No	No
US EPA	2011			Pesticides sales and usage	No	No
Eustis	1994			Multiple-section histo sampling	No	No
FAO	2000			Review	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Farm Chemicals International	2015			Crop protection database	No	No
Ferreira	2010	oxidative stress		Not a relevant human model—fish	No	No
Forgacs	2012			Model for evaluation of reproductive and developmental toxicants	No	No
Freedonia	2012			Industry forecast	No	No
Frescura	2013			Not a relevant human model—fish, glyphosate used as a positive control	No	No
Geret	2013	genotoxicity		Not a relevant human model—oyster	No	No
Gholami-Seyedkolaei	2013	genotoxicity		Not a relevant human model—fish	No	No
Glusczuk	2011	oxidative stress		Not a relevant human model—fish	No	No
Glyphosate Task Force	2014			Glyphosate use	No	No
Granby	2001			Development of a method to measure glyphosate in cereal	No	No
Guha	2013			Residential pesticide use	No	No
Gui	2012			Neurotoxic effects, parkinsonism	No	No
Guilherme	2010	genotoxicity		Not a relevant human model—eel	No	No
Guilherme	2012a	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2012b	oxidative stress		Not a relevant human model—fish	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Guilherme	2014a	oxidative stress		Not a relevant human model—fish	No	No
Guilherme	2014b	genotoxicity		Not a relevant human mode—fish	No	No
Hardell	1999	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
Hardell	2002	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
HaYes	1991			Handbook of pesticide toxicology	No	No
Hidalgo	2004			Liquid chromatographic method in water	No	No
Hilton	2012			Global glyphosate market	No	No
Humphries	2005			Residues in atmosphere, soil and water	No	No
IARC	2006			Data for the monographs	No	No
IARC	2014			Key characteristics of carcinogens	No	No
IPCS	1994			Glyphosate environmental health criteria	No	No
IPCS	1996			Glyphosate data sheet	No	No
IPCS	2005			Glyphosate safety card	No	No
Jacob	1988			Metabolism of glyphosate in pseudomonas	No	No
Jan	2009			Residues measured by spectrophotometric method	No	No
Jauhaianen	1991			Occupational exposure	No	No
Johnson	2005			Occupational exposure	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Kalyanaraman	2012			Measuring reactive oxygen and nitrogen species method	No	No
Kavlock	2012			EPA toxcast program	No	No
Kojima	2004	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Kojima	2010	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Kolpin	2006			Glyphosate and AMPA in US streams	No	No
Kreutz	2011			Not a relevant human model—catfish	No	No
Kuang	2011			Analytical methods for determination of herbicides in food	No	No
Kumar	2014			Not relevant to carcinogenicity classification	No	No
Lavy	1992			Occupational exposure	No	No
Lee	2001			Methods of determination in water	No	No
Lopes	2014			Not relevant to carcinogenicity classification, not a relevant human model—fish	No	No
Lubick	2009			Environmental impact of the cocaine strategy	No	No
Lushchak	2009	oxidative stress		Not a relevant human model—goldfish	No	No
Mahendrakar	2014			Effects and treatment of poisoning	No	No
Malatesta	2008	cytotoxicity		Uses round-up formulation	No	No
Mance	2012			Magazine article, not relevant to carcinogenicity classification	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Mariager	2013			Acute effects, not relevant to carcinogenicity classification	No	No
Marques	2014	genotoxicity		Not a relevant human model—fish	No	No
Marques	2015	genotoxicity		Not a relevant human model—fish	No	No
Maza-Joya	2013	genotoxicity		Not a relevant human model—frogs	No	No
McDuffie	2001	carcinogenicity	Yes	Already reviewed by OCS	Yes	Yes
McQueen	2012			Maternal and prenatal exposure in communities	No	No
Ministry of Chemicals & Fertilizers	2008			Industry performance report	No	No
MLHB	2013			Measurement of glyphosate in human urine samples	No	No
Modesto	2010a	oxidative stress		Not a relevant human model—fish	No	No
Modesto	2010b	oxidative stress		Not a relevant human model—fish	No	No
Mohamed	2011	immune response		Not a relevant human model—freshwater snail	No	No
Moreno	2014	genotoxicity		Not a relevant human model—fish	No	No
Mortensen	2000			Effects and treatment of poisoning	No	No
Motojyuku	2008			Measurement of glyphosate in human serum by GC-MS	No	No
Muangphra	2014	genotoxicity		Not a relevant human model—earthworm	No	No
Nakashima	2002	immune		Not relevant to carcinogenicity classification	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
		response				
NCBI	2015			Open chemistry database	No	No
Nedelkoska	2004			HPLC of glyphosate in water	No	No
Nordstrom	1998	carcinogenicity		Already reviewed by OCS	Yes	No
NPIC	2010			Fact sheet	No	No
Nwani	2013	oxidative stress		Not a relevant human model—fish	No	No
Omran	2013	endocrine disruption		Not relevant for carcinogenicity classification	No	No
Ortiz-Ordonez	2011			Not a relevant human model—fish	No	No
Paganelli	2010	teratology		Not a relevant human model—frogs	No	No
Park	2013			Effects and treatment of poisoning	No	No
Perry	2014			Reporting of exposures to pesticides in the UK	No	No
Pesticides Residues Committee	2007			Pesticide monitoring report	No	No
Pesticides Residues Committee	2008			Pesticide monitoring report	No	No
Pesticides Residues Committee	2010			Pesticide monitoring report	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Piola	2013	toxicity		Not a relevant human model—earthworm	No	No
Poletta	2009	genotoxicity		Not a relevant human model—caiman	No	No
Poletta	2011	genotoxicity		Not a relevant human model—caiman	No	No
Republica de El Salvador	2013			Notice on prohibited pesticides	No	No
Roberts	2010			Effects and treatment of poisoning	No	No
Rueppel	1977			Metabolism of glyphosate in soil and water	No	No
Rumack	2015			Effects and treatment of poisoning	No	No
Sanchis	2012			Glyphosate in groundwater	No	No
Siddiqui	2012	genotoxicity		Not a relevant human model—fenugreek	No	No
Simonsen	2008			Glyphosate and AMPA in soil	No	No
Sinhorin	2014	oxidative stress		Not a relevant human model—fish	No	No
Slaninova	2009	oxidative stress		Not a relevant human model—fish	No	No
Sorensen	1999			Effects and treatment of poisoning	No	No
Sribanditmongkol	2012			Effects and treatment of poisoning	No	No
Stella	2004			Effects and treatment of poisoning	No	No
Szekacs	2012			Book about control of weeds	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
Temple	1992			Effects and treatment of poisoning	No	No
Thongprakaisang	2013	endocrine disruption		Not relevant for carcinogenicity classification	No	No
Tian	2012			Synthetic alternative to glyphosate	No	No
Tice	2013			Human hazard characterisation of chemicals	No	No
Tomlin	2000			Pesticide manual	No	No
Transparency Market Research	2014			Global glyphosate market	No	No
Truta	2011	genotoxicity		Not a relevant human model—barley	No	No
Tu	2001			Weed control handbook	No	No
Uren Webster	2014	reproductive/ developmental		Not a relevant human model—fish	No	No
Vasiluk	2005			Oral bioavailability of glyphosate in vitro	No	No
Vera-Candioti	2013	genotoxicity		Not a relevant human model—fish	No	No
Walsh	2000	reproductive/ developmental		Not relevant to carcinogenicity classification	No	No
Wang	2012	genotoxicity		Not a relevant human model—cyanobacterium	No	No
Wester	1991			Not relevant to carcinogenicity classification, dermal absorption	No	No
Xie	2005	endocrine		Not relevant to carcinogenicity classification, not a relevant human	No	No

Author	Year	Endpoint	Epidemiology study?	Reason for exclusion	Evaluated by	
					OCS	EU (2013)
		disruption		model—fish		
Yadav	2013	genotoxicity		Not a relevant human model—tadpoles	No	No
Yin	2011			Glyphosate use review	No	No
Yoshioka	2011			Measurement of glyphosate by liquid chromatography	No	No
Zahm	1990	carcinogenicity	Yes	2,4-D study	No	No
Zhao	2013	endocrine disruption		Not relevant to carcinogenicity classification	No	No
Zouaoui	2013			Effects and treatment of poisoning	No	No

ABBREVIATIONS

ADI	Acceptable daily intake (for humans)
ADME	Absorption, distribution, metabolism and excretion
AER	Adverse Experience Report
AERP	Adverse Experience Reporting Program
Agvet Code	Agricultural and Veterinary Chemicals Code, Schedule to the *Agricultural and Veterinary Chemicals Code Act 1994*
AHS	Agricultural Health Survey
AMPA	Aminomethylphosphonic acid
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute reference dose
ATDS	Australian Total Diet Survey
BfR	Federal Institute for Risk Assessment
CAT	Catalase
CHO-HGPRT	Chinese Hamster Ovary-Hypoxanthine-Guanine Phosphoribosyl Transferase
CLH	Harmonised classification
CI	Confidence Interval
CLP criteria	Classification, Labelling and Packaging of Substances and Mixtures
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EOS	Earth Open Source
EP	European Parliament
EPSPS	Enzyme 5-enolpyruvylshikimate-3-phosphate synthase
EU	European Union
FAO	Food and Agriculture Organisation

FRAP	Ferric-inducing ability of plasma
FSANZ	Food Standards Australia New Zealand
GLP	Good laboratory practice
GSH	Glutathione
GST	Glutathione-S-transferase
HIV	human immunodeficiency virus
hOGG1	Human 8-oxoguanine DNA N-glycosylase 1
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	Kilogram
L	Litre
LD_{50}	Lethal dose
MCPA	2-methyl-4-chlorophenoxyacetic acid
MEPs	Members of the European Parliament
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
mg/L	Milligrams per litre
MRL	Maximum residue limit
NHL	Non-Hodgkin's lymphoma
NHMRC	National Health and Medical Research Centre
NOAEL	No observed adverse effect level
NRA	National Registration Authority
NRS	National Residue Survey
OCS	Office of Chemical Safety
OECD	The Organisation for Economic Co-operation and Development
OECD TGs	OECD Testing guidelines
8-OHdG	8-hydroxy-2'-deoxyguanosine

OR	Odds Ratio
PMRA	Pest Management Regulatory Agency
POEA	Polyethoxylated tallow amine (or polyoxyethylated tallow amine and various synonyms)
RAR	Renewal assessment rapport
RMS	Rapporteur member state
ROS	Reactive oxygen species
RR	Risk ratio
SCE	Sister chromatic exchange
SCGE	single cell gel electrophoresis
SOD	Superoxide dismutase
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TBARS	Thiobarbituric acid reactive substances
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
US EPA	US Environmental Protection Agency
US FDA	US Food and Drug Administration
WHO	World Health Organization

GLOSSARY

Acceptable daily intake	A level of intake of a chemical that can be ingested daily over an entire lifetime without any appreciable risk to health
Acute reference dose	The estimated amount of a substance in food or drinking-water, (expressed on a body weight basis), that can be ingested or absorbed over 24 hours or less, without appreciable health risk
Benchmark dose	A dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; the dose associated with a specified measure or change of
Lethal dose	The amount of an ingested substance that kills 50 per cent of a test sample
Maximum residue limit	The highest concentration of a chemical residue that is legally permitted in a food
No observed adverse effect level	Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure

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Exhibit 1020

I, Scott Jeror, Publications Supervisor in the
Policy, Communications and Regulatory Affairs Directorate
of the Pest Management Regulatory Agency of Health Canada,
hereby certify that the attached document,
"Re-evaluation Decision RVD2017-01, *Glyphosate*",
dated April 28, 2017,
is a true copy of the original document.

Scott Jeror

Signed before me on May 18, 2018

Nicole Levasseur

Re-evaluation Decision RVD2017-01

Glyphosate

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Table of Contents

Executive Summary

Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency (PMRA) before they can be imported, sold, or used in Canada. Pesticides must go through rigorous science-based assessments before being approved for sale in Canada.

All registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environment safety standards and continue to have value. In 2015, the PMRA published the outcome of its extensive re-examination of glyphosate for public comment (PRVD2015-01), which concluded that the products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the revised product label directions.

During this re-examination, the PMRA assessed the potential human health risk of glyphosate from drinking water, food, occupational and bystander exposure, as well as the environmental risk to non-target organisms. Both the active ingredient and formulated products were included in the re-evaluation. The assessment was carried out based on available information provided by the manufacturer of the pesticide, as well as a large volume of published scientific literature, monitoring information (for example, ground water and surface water) and reviews conducted by other regulatory authorities.

The overall finding from the re-examination of glyphosate is highlighted as follows:

- Glyphosate is not genotoxic and is unlikely to pose a human cancer risk.
- Dietary (food and drinking water) exposure associated with the use of glyphosate is not expected to pose a risk of concern to human health.
- Occupational and residential risks associated with the use of glyphosate are not of concern, provided that updated label instructions are followed.
- The environmental assessment concluded that spray buffer zones are necessary to mitigate potential risks to non-target species (for example, vegetation near treated areas, aquatic invertebrates and fish) from spray drift.
- When used according to revised label directions, glyphosate products are not expected to pose risks of concern to the environment.
- All registered glyphosate uses have value for weed control in agriculture and non-agricultural land management.

All comments received during the consultation process were taken into consideration. These comments and new data/information resulted in only minor revisions to the proposed regulatory decision described in PRVD2015-01. Therefore, the PMRA is granting continued registration of products containing glyphosate with requirements of additional label updates to further protect human health and the environment.

To comply with this decision, the required label changes must be implemented on all product labels sold by registrants no later than 24 months after the publication date of this document.

Re-evaluation Decision for Glyphosate

After a re-evaluation of the herbicide glyphosate, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting continued registration of products containing glyphosate for sale and use in Canada.

An evaluation of available scientific information found that products containing glyphosate do not present risks of concern to human health or the environment when used according to the revised label directions. As a requirement for the continued registration of glyphosate uses, new risk reduction measures are required for the end-use products registered in Canada. No additional data are being requested at this time.

Findings of the re-evaluation of glyphosate were first presented for public consultation in the Proposed Re-evaluation Decision PRVD2015-01, *Glyphosate*,[1] whereas this Re-evaluation Decision (RVD2017-01)[2] summarizes the Agency's final decision on the re-evaluation of glyphosate and the reasons for it.

Comments received during the consultation period were taken into consideration. These comments and new data/information resulted in revisions to some parts of the risk assessments, however, they did not result in substantial changes to the proposed regulatory decision as described in PRVD2015-01. Appendix I of this document summarizes the comments received and provides the PMRA's response.

To comply with this decision, the required mitigation measures must be implemented on all product labels sold by registrants no later than 24 months after the publication date of this document. Registrants of the products containing glyphosate will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

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

Health Canada's pesticide re-evaluation program considers potential risks[3] as well as the value[4] 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.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "…the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

In 2010, Health Canada published a re-evaluation work plan for glyphosate (REV2010-02) outlining the focus of this re-evaluation and indicating that the PMRA is working cooperatively with the United States Environmental Protection Agency. As part of this re-evaluation, the effect of Polyethoxylated Tallow Amines (POEA) and the metabolite and transformation product Aminomethylphosphonic acid (AMPA) are also included.

What Is Glyphosate?

Glyphosate is a broad-spectrum, non-selective herbicide. It controls many annual weeds, perennial weeds, woody brush and weedy trees. It is registered for use on a wide variety of sites including terrestrial feed and food crops, terrestrial non-food, non-feed and fibre crops, and for non-agricultural, industrial and residential weed management for non-food sites, forests and woodlots, outdoor ornamentals and turf.

Glyphosate is present as the free acid or as a salt in formulated end use products. Glyphosate products are formulated as solutions, pastes or tablets and can be applied using ground or aerial application equipment. Other application techniques are also used to apply glyphosate, such as with a wiper or wick applicator, cut stump or stem injection treatment. The rate of application ranges from 0.25 to 4.32 kg a.e./ha, depending on weed species (for example, annual vs. perennial) and use site. All products containing glyphosate currently registered under the authority of the *Pest Control Products Act* are listed in Appendix II.

Health Considerations

Can Approved Uses of Glyphosate Affect Human Health?

Products containing glyphosate are unlikely to affect your health when used according to label directions.

Potential exposure to glyphosate may occur through diet (food and water), or when handling and applying the product, or by entering treated sites. When assessing health risks, two key factors are considered: 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 those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Glyphosate is of low acute oral, dermal and inhalation toxicity. It is severely irritating to the eyes, non-irritating to skin and does not cause an allergic skin reaction.

Registrant-supplied short and long term (lifetime) animal toxicity tests, as well as numerous peer-reviewed studies from the published scientific literature were assessed for the potential of glyphosate to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects.

The most sensitive endpoints for risk assessment were clinical signs of toxicity, developmental effects, and changes in body weight. The young were more sensitive than the adult animals. However, the risk assessment approach ensures that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food and Water

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Potential acute and chronic dietary exposures to glyphosate were estimated from residues of glyphosate and relevant metabolites in both treated crops and drinking water. Exposure to different subpopulations, including children and women of reproductive age, were considered. The acute dietary exposure estimate from food and drinking water at the 95th percentile represents 31% of the acute reference dose (ARfD) for females 13-49 years of age, and ranges from 12% to 45% of the ARfD for all other population subgroups. The chronic dietary exposure estimate for the general population represents 30% of the acceptable daily intake (ADI). Exposure estimates for population subgroups range from 20% of the ADI (for adults aged 50 years or older) to 70% of the ADI (for children 1-2 years old). Thus, acute and chronic dietary risks are not of concern.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose a health risk concern.

Canadian MRLs for glyphosate are currently specified for a wide range of commodities (MRL database http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specific MRL, are regulated under Subsection B.15.002(1) of the Food and Drug Regulations, which requires that residues do not exceed 0.1 ppm. Separate MRLs have been established for the trimethylsulfonium (TMS) cation, the major metabolite of the glyphosate-TMS salt, in/on a variety of commodities. Given that all glyphosate-TMS-containing products have been discontinued in Canada, all MRLs for the TMS cation will be revoked.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern when used according to label directions.

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

Residential postapplication exposure may occur for persons performing activities on treated areas. This includes areas treated by residential handlers as well as residential areas treated by commercial applicators. Exposure is predominantly dermal. Incidental oral exposure may also occur for children (1 to <2 years old) playing in treated areas.

For all domestic class products, the target dermal and inhalation margins of exposure (MOE) were met for adults applying glyphosate and are not of concern. Residential postapplication activities also met the target dermal MOE for all populations (including golfers) and are not of concern. For incidental oral exposure, the target oral MOEs were met for children (1 to <2 years old) and are not of concern.

Non-occupational scenarios were aggregated with background (chronic) dietary exposure (food and drinking water). The resulting aggregate risk estimates reached the target MOE for all uses and are not of concern.

Non-occupational risks from bystander dermal exposure are not of concern.

Bystander exposure may occur when the general public enter non-cropland areas (for example, hiking through forests or parks) that have recently been treated with glyphosate. The resulting risk estimates associated with bystander dermal exposure met the target MOE for all populations and are not of concern.

Occupational Risks from Handling Glyphosate

Occupational risks to handlers are not of concern when used according to label directions.

Risks to handlers are not of concern for all scenarios. Based on the precautions and directions for use on product labels reviewed for this re-evaluation, risk estimates associated with mixing, loading and applying activities met the target dermal and inhalation MOEs and are not of concern.

Postapplication risks are not of concern for all uses.

Postapplication occupational risk assessments consider exposures to workers entering treated sites in agriculture. Based on the current use pattern for agricultural scenarios reviewed for this re-evaluation, postapplication risks to workers performing activities, such as scouting, met the target dermal MOEs and are not of concern. A minimum restricted entry interval of 12 hours is required for agricultural sites.

Polyethoxylated Tallow Amines (POEA)

POEA is a family of several compounds that are used as surfactants in many glyphosate products registered in Canada. No human health risks of concern were identified for these end-use products, provided that they contain no more than 20% POEA by weight. All of the currently registered glyphosate end-use products in Canada meet this limit.

Environmental Considerations

What Happens When Glyphosate Is Introduced Into the Environment?

When used according to revised label directions, glyphosate products are not expected to pose risks of concern to the environment. Labelled risk-reduction measures mitigate potential risks posed by glyphosate formulations to non-target plants and freshwater/marine/estuarine organisms.

When glyphosate is released into the environment, it can enter soil and surface water. Glyphosate breaks down in soil and water and is not expected to remain for long periods of time. Glyphosate produces one major break down product in soil and water, aminomethyl phosphonic acid (AMPA), which can last 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 remain in the environment. While, in general, glyphosate formulations that contain POEA are more toxic to freshwater and marine/estuarine organisms than formulations that do not contain POEA, they do not pose risks of concern to the environment when used as directed on the label.

In the terrestrial environment the only risk identified was for terrestrial plants, therefore, spray buffer zones are required to reduce exposure to sensitive terrestrial plants.

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.

Glyphosate, AMPA and POEA do not meet all Toxic Substances Management Policy (TSMP) Track 1 criteria and are not considered Track 1 substances. Other than incident reports of damage to plants and one exceptional incident regarding fish in a river (PRVD2015-01, Section 4.2.3), there are currently no environmental incident reports involving glyphosate in Canada.

Value Considerations

What is the 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.

Glyphosate is an important herbicide for Canadian agriculture:

- Due largely 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 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 agricultural production practice in Canada.
- It has a wide application window ranging from pre-seeding to after seeding (prior to crop emergence), in-crop, pre-harvest or post-harvest, providing a flexible and effective weed management program.
- It is one of a few herbicides that can also be used as a harvest management and desiccation treatment.
- Post-harvest stubble treatment with glyphosate allows reduced or zero tillage, which has facilitated the adoption of conservation agriculture that results in improved soil quality.

Glyphosate is also an important weed management tool and is widely used for weed control in non-agricultural land management, such as forestry, industrial areas, and along rights-of-way. It is an effective tool for control of many invasive weed species and is also used in the control of toxic plants, such as poison ivy.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of glyphosate, the PMRA is requiring further risk-reduction measures in addition to those already listed on glyphosate product labels.

Additional risk-reduction measures are discussed below. Label amendments to be implemented are found in Appendix IV.

Human Health

- To protect commercial and residential applicators: glyphosate is not to be applied using hand-wicking or hand-daubing methods.
- To protect workers entering treated sites: a restricted-entry interval (REI) of 12 hours is required for agricultural uses.
- To protect bystanders: a statement is required indicating that the product is to be applied only when the potential for drift to areas of human habitation or areas of human activity, such as houses, cottages, schools and recreational areas, is minimal.

Environment

- Environmental hazard statements are added to inform users of toxicity to non-target species.
- Spray buffer zones to protect non-target terrestrial and aquatic habitats are required.
- To reduce the potential for runoff of glyphosate to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required. In addition, a vegetative strip between the treatment area and the edge of a water body is recommended to reduce runoff of glyphosate to aquatic areas.

What Additional Scientific Information is Being Requested?

There are no additional data requirements proposed as a condition of continued registration of glyphosate products.

International Regulatory Status and Updates on Glyphosate

The PMRA routinely works collaboratively with other member countries within the Organisation for Economic Co-operation and Development (OECD) on the regulation of pesticides. As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of a pesticide in other jurisdictions. Glyphosate is currently acceptable for use in other OECD countries, including the United States, Australia and the European Union. As of 8 March 2017, no decision by an OECD member country to prohibit all uses of glyphosate for health or environmental reasons has been identified.

In March, 2015, the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) published a summary of results of their hazard classification of five pesticides, including glyphosate. IARC classified glyphosate as probably carcinogenic to humans. It is important to note that the IARC classification is a hazard classification and not a health risk assessment. This means that the level of human exposure, which determines the actual risk, was not taken into account by IARC.

In November, 2015, the European Food Safety Authority (EFSA) finalized their re-assessment of glyphosate, concluding that glyphosate is unlikely to pose a carcinogenic hazard to humans. The EU also set an acute reference dose, which is the same as that set by the PMRA (PRVD2015-01). In May 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures and that it is unlikely to pose a carcinogenic risk to humans from exposure through the diet. In March, 2017, the European Chemical Agency (ECHA) and the Australian Pesticides and Veterinary Medicines Authority (APVMA) released their determination that glyphosate is not a carcinogen. Currently, no pesticide regulatory authority, including Health Canada, considers glyphosate to be a carcinogenic risk of concern to humans.

Canada and the USEPA have been collaborating on the re-evaluation of glyphosate. In December 2016, the USEPA Scientific Advisory Panel (SAP) discussed the cancer potential of glyphosate, and Health Canada's PMRA participated as an observer. The final SAP meeting report was posted on March 17, 2017. The PMRA is continuing to monitor regulatory activities from other regulatory organizations, including the USEPA's review of the SAP recommendations and final determination regarding the potential carcinogenicity of glyphosate.

Health Canada's PMRA sets Maximum Residue Limits (MRLs) for pesticide residues on food, which is the maximum amount of residue that is expected to remain on food products when a pesticide is used according to label directions. These are set at levels well below the amount that could pose a health concern. In 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having the full analysis completed by Spring 2017.

Other Information

Any person may file a notice of objection regarding this decision on glyphosate within 60 days from the date of publication of Re-evaluation Decision RVD2017-01, *Glyphosate*. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision), or contact the PMRA's Pest Management Information Service.

List of Abbreviations

AD	administered dose
ADI	allowable daily intake
a.e.	acid equivalent
AFC	antibody forming cells
AHS	agricultural health study
AMPA	aminomethylphosphonic acid
APVMA	Australian Pesticide and Veterinary Medicines Authority
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
ATAE	phosphate ester, tallowamine, ethoxylated
Atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
Bt	*Bacillus thuringiensis*
BVL	The German Federal Office for Consumer Protection and Food Safety
CARC	Cancer Assessment Review Committee
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
CHMS	Canadian Health Measures Survey
Cm	centimeter
DACO	Data Code
DAR	Draft Assessment Report
DIR	Directive
DMTT	PMRA drift mitigation technical team
DT_{50}	time required for 50% dissipation of the initial concentration
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ECx	effective concentration on x (any number) % of the population
ECHA	European Chemicals Agency
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EDTA	Endocrine Disrupters Testing and Assessment
EFSA	European Food Safety Authority
EP	end-use product
EU	European Union
EUP	end-use product
EUP + POEA	end-use products containing the surfactant POEA
EUP NO POEA	end-use products that do not contain POEA
FA	fraction of species affected
FAO	Food and Agriculture Organization of the United Nations
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GLP	Good Laboratory Practices
GMO	genetically modified
Ha	hectare(s)

HC_5	hazardous concentration to five percent of species in a Species Sensitivity Distribution (SSD)
HD_5	hazardous dose to five percent of species in a Species Sensitivity Distribution (SSD)
Hr	hour(s)
HL	Hodgkin's lymphoma
IARC	International Agency for Research on Cancer
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgM	Immunoglobulin M
IPA salt	isopropylamine salt
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JGTF	Joint Glyphosate Task Force
JMPR	Joint WHO/FAO Meeting on Pesticide Residues
K_{ow}	*n*-octanol-water partition coefficient
L	litre
Lab	laboratory
LC_{50}	lethal concentration on 50% of the population
LC_x	lethal concentration on x (any number) % of the population
Log	logarithm
LOAEL	lowest observed adverse effect level
m^3	meter cube
mg	milligram
mm	millimeter
Mn	Manganese
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MWCF	Molecular Weight Conversion Factor
N. bruchi	*Neochetina bruchi*
Ng	nanogram
NHL	Non-Hodgkin Lymphoma
NOAEL	no observed adverse effect level
NOEC	no-observed-effect-concentration
NOEL	no-observed-effect-level
NOI	notice of intent
NPAFC	North Pacific Anadromous Fish Commission
NTP	National Toxicology Program
NZEPA	New Zealand Environmental Protection Authority
OECD	Organization for Economic Co-operation and Development
OPP	Office of Pesticides
Pa	pascal
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
POEA	Polyethoxylated tallow amines
PPE	Personal Protective Equipment
ppm	parts per million

PRVD	Proposed Re-evaluation Decision
RAR	Renewal Assessment Report
ROS	reactive oxygen species
RD	Residue Definition
RED	Reregistration Eligibility Decision
REG	Regulatory Note
REI	Restricted-Entry Interval
REV	Re-evaluation Note
RVD	Re-evaluation Decision
SAP	Scientific Advisory Panel
SPN	Science Policy Note
spp.	species (plural)
SSD	species sensitivity distribution
Tech.	technical
TGAI	technical grade active ingredient
TSMP	toxic substances management policy
TTR	Turf Transferable Residue
UK	United Kingdom
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
VMG	Validation Management Groups
WHO	World Health Organization

Appendix I Comments and Responses

The PMRA received written comments from the technical registrants, the public and other stakeholders relating to the *Proposed Re-evaluation Decision PRVD2015-01, Glyphosate*. The comments and PMRA responses are summarized based on common scientific themes.

1.0 Comments Related to the Health Risk Assessments

1.1 Comments Related to Toxicology

In addition to specific comments related to the toxicological evaluation of glyphosate, comments related to broader considerations, were also received. These broader comments included questions on the established paradigms for the toxicological evaluation of chemicals in general, comments on the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, concerns relating to the independence of the scientific findings, principles of Good Laboratory Practices (GLP), and other aspects of toxicological assessments. Although these broader types of comments were beyond the scope of the re-evaluation of glyphosate, every effort has been made to respond to the underlying concerns in the submitted comments as they relate to the toxicology review and health aspects of the glyphosate re-evaluation in Canada.

1.1.1 Salivary gland alterations and Acceptable Daily Intake (ADI)

Comment
The Joint Glyphosate Task Force (JGTF) proposed that the observation of cellular alterations in salivary glands results from oral irritation caused by dietary administration of glyphosate acid – a strong organic acid. New data was submitted to support this conclusion. In addition, it was noted that Canadian glyphosate formulations do not contain the technical acid, but instead contain neutral glyphosate salts (for example, potassium, ammonium, and isopropylamine). The JGTF requested that the PMRA consider the new data, re-assess the adversity of this finding, and base the ADI calculation on a more toxicologically relevant No Observed Adverse Effect Level (NOAEL).

PMRA Response
The newly submitted data consisted of a dose-range finding study and a non-guideline definitive study that examined the effects of citric acid administered to rats via gavage (to bypass direct oral exposure) or via diet, and trisodium citrate dihydrate given via diet for seven weeks. Rats treated with citric acid in their diet (a low pH diet) exhibited more pronounced changes in parotid glands (increased weight and histopathology severity) compared to rats receiving citric acid via gavage, or trisodium citrate dihydrate by diet (high pH diet).

However, an acidic diet did not appear to be the only factor responsible for changes in parotid glands, since these changes (albeit less pronounced) were also observed in both the high pH diet and gavage-treated citric acid (low pH) groups. Also, other organizations have conducted studies examining different modes of action (MOAs) that might explain changes observed in salivary glands of animals fed glyphosate-treated diets.

For example, as discussed in PRVD2015-01, (page 12), studies by the National Toxicology Program (NTP) indicated that glyphosate may be a β-adrenergic receptor agonist, as histological similarities were noted in salivary glands of animals treated with glyphosate acid, or a β-adrenergic receptor agonist (isoproterenol), and were reduced in severity by propranolol (a β-adrenergic receptor antagonist).

Additionally, the hazard assessment was based on the 'active substance' (glyphosate acid). Guideline toxicity data for "neutral" glyphosate salts, with particular attention to salivary gland examination in repeat-dose studies, were not available for selection of the toxicity endpoints.

The toxicological evaluation relied on a number of co-critical studies, rather than one 'key study', to establish each endpoint. The ADI (PRVD2015-01, page 20) is based on a 2-year study in rats with a NOAEL of 32/34 mg/kg bw/day, the highest (combined) NOAEL for all 2-year rat studies. The lowest (combined) Lowest Observed Adverse Effect Level (LOAEL) is 100 mg/kg bw/day, based on decreased body weight and increased incidences and severity of cellular alterations in the parotid and submandibular glands in one of the two-year rat studies. This choice of NOAEL and LOAEL is further supported by the NOAEL of 30 and LOAEL of 100 mg/kg bw/day, based on decreased body weight in three one-year dog studies. Thus, the selected ADI is based on two primary findings (decreased body weight as well as histological changes in the parotid salivary gland) observed in a number of different studies. No revision is required.

1.1.2 Acute Reference Dose (ARfD) for females 13-49 years of age

Comment
The endpoint selected for the ARfD for females 13-49 years of age was considered by the JGTF to be based on a spurious finding that is not reflected across developmental toxicity studies of glyphosate in rabbits. The JGTF presented an evaluation of seven rabbit developmental toxicity studies conducted by Kimmel et al. (2013), which concluded that the body of data failed to support an increased incidence of interventricular septal defects in the fetuses resulting from treatment with glyphosate during gestation in rabbits. Overall, the JGTF requested that the ARfD for this subpopulation be aligned with the ARfD for the general population.

PMRA Response
As noted in PRVD2015-01, the PMRA considered the evaluation conducted by Kimmel et al. (2013) in detail, as well as other available information, and based its conclusion on the overall weight-of-evidence in establishing an ARfD for the subpopulation of females 13-49 years of age.

Briefly, several limitations were noted in the analysis by Kimmel et al. (2013) including data tabulation errors and a lack of, or inadequately characterized, historical control data for key studies, including the study on which the PMRA based the ARfD. A re-analysis of this key study (Brooker et al. 1991, PMRA #1161779; PRVD2015-01) in conjunction with additional historical control data supplied by the JGTF resulted in the PMRA concluding that the incidence of cardiac malformations was increased relative to both concurrent and historical control data in high-dose animals, with an increase in variations at the mid-dose. The additional historical data provided by the JGTF did not alter the PMRA's original conclusions, thus, the ARfD for females 13-49 years of age was not revised.

1.1.3 Cancer Risk Assessment

Comments

1.1.3.1 International Agency for Research on Cancer (IARC) Glyphosate Monograph[5]

The majority of comments in relation to the 2015 IARC assessment, which classified glyphosate as 'probably carcinogenic to humans', requested that the PMRA review and re-assess the potential carcinogenicity of glyphosate, and restrict/ban its uses in Canada. Some comments noted that while the IARC assessment is a hazard classification, it also took into account the human exposure levels to glyphosate, largely by incorporating the epidemiological studies into the assessment. Some comments recommended that the PMRA apply the IARC classification in selecting a sensitive endpoint for occupational and bystander risk assessment in order to protect against the risk of developing non-Hodgkin's lymphoma and/or other cancers.

1.1.3.2 Ovarian Tubulostromal Tumours

The JGTF noted that PRVD2015-01 reported an increased incidence of ovarian tubulostromal tumours. The JGTF stated that these neoplasms arise out of the germinal epithelium of the ovarian stroma, are similar to those seen in epithelial hyperplasia, and therefore, do not provide sufficient evidence for oncogenicity. They also provided historical control data relevant to the strain of mice used, and noted that the reported incidence was within the range of Charles River historical control data for this finding. The JGTF requested that PMRA consider this finding as not related to glyphosate treatment and revise the text on page 89 of PRVD2015-01 from "equivocal evidence of oncogenicity" to "no evidence of oncogenicity"

1.1.3.3 Agricultural Health Study and Multiple Myeloma

The JGTF requested that the PMRA reconsider the suggested association between multiple myeloma and glyphosate use that was reported by the Agricultural Health Study (AHS) publication (De Roos et al. 2005, PMRA#:2391583). The comments indicated that it has been over 10 years since the study was conducted and a follow-up study, noted by De Roos as being necessary, has not been performed. The JGTF also noted that in an effort to understand how the conclusion of 'suggested association' was reached in the AHS study, the data were analyzed by a third-party expert (Sorahan, 2015) who determined that De Roos et. al., 2005 had pared down the AHS data set to come to the conclusion of 'suggested association'. When the full data set is analyzed, the risk ratio is 1.1, demonstrating no association between multiple myeloma and glyphosate use. Additionally, no association between multiple myeloma and glyphosate use was noted by the IARC review of glyphosate, which considered the Sorahan (2015) paper.

[5] IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112 (2015). Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. Available online from http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf [last accessed June, 2016]

PMRA Response to Comments 1.1.3.1 – 1.1.3.3

Background

In March, 2015, the International Agency for Research on Cancer (IARC) published a summary of the basis for their hazard classifications of five pesticides, including glyphosate, which they classified as 'probably carcinogenic to humans'. The PMRA's position on the IARC's hazard-based classification was included in PRVD2015-01, published in April, 2015, however, the full IARC monograph only became available in July, 2015. The PMRA has since reviewed this document; a summary of the PMRA review is discussed below.

The IARC Assessment

The PMRA and IARC assessments of the carcinogenic potential of glyphosate were based on different datasets and considerations. As noted in Re-evaluation Note 2010 (REV2010-02), the PMRA collaborated with the United States Environmental Protection Agency (USEPA) on the re-evaluation of glyphosate, which included the examination of published scientific toxicity data according to the principles set out in USEPA guidance.[6] Additionally, considerations laid out in a second USEPA guidance[7] document were applied in the review of published epidemiology data.

The carcinogenic potential of glyphosate acid, the technical active ingredient, was assessed by the PMRA using a weight-of-evidence approach. Many registrant-supplied studies are available on the carcinogenic potential of glyphosate, which include lifetime cancer bioassays, as well as in vitro and in vivo mutagenicity studies. In addition, published data as well as epidemiological data were available for consideration. Results were then integrated and weighed according to their reliability, relevance and consistency. Note that studies conducted with glyphosate alone were considered more relevant in characterizing its inherent toxicity than were studies on the formulated products reported in the scientific literature, as the latter contained a variety of other constituents that, in most cases, were not identified. The compositions of formulated products are considered proprietary data, and often differ between countries. However, the composition of the formulated products must be disclosed to regulatory authorities in the country of registration; (see Genotoxicity section below). Although it is argued that formulated glyphosate products are more representative of 'real life' conditions, it is important to keep in mind that many different products (pesticide and non-pesticide) share many of these same constituents. In order to fully characterize a pesticide active ingredient, it is necessary to understand its inherent toxicity, which can only be characterized in the absence of these other constituents.

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6 EPA (U.S. Environmental Protection Agency), 2012, Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf [last accessed February, 2016]

7 EPA (U.S. Environmental Protection Agency), 2010, February 2010 FIFRA SAP meeting minutes: Draft Framework and Case studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment. Available online from https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0125-0079 [last accessed February 2016]

In addition, studies that complied with internationally accepted test guidelines were considered by the PMRA to be more relevant and reliable than published studies conducted with methodologies not recognized by regulatory agencies or organizations, such as the OECD. In total, the PMRA, in cooperation with the USEPA, assessed a much larger and more relevant body of scientific information than was considered by the IARC.

Conversely, in its evaluation of the carcinogenic potential of glyphosate, the IARC considered only published sources of toxicology data, which included the scientific literature and certain documents published by regulatory agencies. The IARC did not directly consider, or did not consider at all, unpublished toxicology studies that were available to international regulatory agencies. It is the PMRA's understanding that unpublished registrant-sponsored studies are not requested by the IARC for their deliberations. Furthermore, the IARC classifications of carcinogenic hazard are based on scientific consensus related to the evidence examined, but do not provide risk information or recommendations for regulation or legislation. The IARC assessment relied on many studies that did not characterize the composition of the tested mixtures (formulated products) and/or grouped all glyphosate formulated products, regardless of their composition. The composition of glyphosate formulated products differs around the world, even in those marketed under the same trade name. This difference in the evaluation approach used by the IARC and the PMRA is an important distinction because some studies, mostly in vitro, with glyphosate formulated products suggest that certain formulations are genotoxic, while studies examining the active substance alone do not show this effect. This may indicate that genotoxicity observed in these studies is related to other constituents in the formulated product rather than glyphosate acid. The constituents of all pest control products registered in Canada are disclosed to the PMRA, and toxicity data (as well as other data) are also required for each formulated product, which are examined during the pre-market review process.

Genotoxicity

The PMRA did not identify any genotoxic potential for the active ingredient glyphosate acid. Negative results for in vitro and in vivo gene mutation and chromosomal effect assays in mammalian cells contributed to the overall conclusion that the active ingredient glyphosate was not genotoxic. In vitro studies are generally conducted to predict a potential effect in animal (in vivo) studies. In vivo studies are weighted more than in vitro studies based on relevancy and integrated metabolism of the whole animal.

A large battery of genotoxicity assays conducted according to the OECD test guidelines for glyphosate is available. Many studies have been replicated several times, and all indicated negative results for genotoxicity. The IARC assessment did not consider the majority of these studies. Instead, the IARC monograph reported mixed results for studies with glyphosate formulated products that examined DNA damage, gene mutation, and chromosomal aberrations, and included results from non-mammalian systems – for example fish, and plants, that are not considered relevant for human health hazard characterization.

The IARC monograph also noted that in several cases, positive results occurred at very high or toxic dose levels only. It is important to characterize the relationship of genotoxic results in the context of observed cytotoxicity. Positive results at very high or toxic dose levels indicate that the genotoxic effects are due to cytotoxicity rather than direct DNA-acting properties of glyphosate formulated products. High-dose cytotoxicity was one factor in the weight-of-evidence

approach used by the PMRA when considering the genotoxic potential of glyphosate, and is consistent with international approaches (EFSA 2011,[8] USEPA 1986,[9] USFDA, ICH S2(R1)[10]). The observed cytotoxicity is likely associated with surfactants that are present in many formulated products. For example, polyethoxylated tallow amines (POEAs), which are typical surfactant components of many glyphosate products, were shown to produce cytotoxic effects such as perturbation/disruption of the mitochondrial membrane in cultured mammalian cells (Levine et al. 2007,[11] Kier and Kirkland 2013[12]). A number of negative genotoxicity studies were reported by Kier and Kirkland (2013), but not considered by the IARC. It should be noted that genotoxic effects resulting from cytotoxicity exhibit a threshold, and carefully selected reference doses protect against this effect.

The IARC suggested other 'mechanisms of action' that might contribute to potential carcinogenicity, such as inflammation, immunosuppression, endocrine disrupting activity and oxidative stress, which were based mainly on in vitro studies. However, no evidence of glyphosate-induced immunosuppression was observed in a registrant-supplied guideline immunotoxicity study reviewed by the PMRA. In addition, no other studies in the extensive toxicity database suggested a concern for immunotoxicity, inflammation or oxidative stress. Glyphosate also showed no evidence of interaction with estrogen, androgen or thyroid endocrine pathways in studies conducted by the USEPA Endocrine Disruptor Screening Program (EDSP).

Carcinogenicity

1. Studies in Animals

As reported in PRVD2015-01, the PMRA also assessed the carcinogenic potential of glyphosate in several long-term animal studies, which included two mouse studies and four rat studies, as well as studies in the published literature. Although, not all available carcinogenicity studies on glyphosate were submitted to the PMRA, reviews, evaluation reports, and committee meeting documents from international regulatory authorities (EFSA and USEPA) for these particular studies were considered by the PMRA. No evidence of carcinogenicity was identified in any of the rat studies reviewed by the PMRA, or in the additional rat studies reviewed by other regulatory authorities.

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8 EFSA (European Food Safety Authority), 2011. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Scientific Committee, EFSA journal, 9, 2379

9 EPA (U.S. Environmental Protection Agency), 1986. Guidelines for mutagenicity risk assessment. Fed. Register 51. 34006-34012.

10 FDA (U.S. Food and Drug Administration), 2012. Guidance for Industry. S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Available online from http://www.fda.gov/downloads/Drugs/Guidances/ucm074931.pdf [last accessed February, 2016]

11 Levine SL, Han Z, Liu J, et al. (2007). Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis. Cell Biology and Toxicology, 23, 385–400. Available online from http://link.springer.com/article/10.1007%2Fs10565-007-9001-6 [last accessed June, 2016]

12 Larry D. Kier & David J. Kirkland (2013) Review of genotoxicity studies of glyphosate and glyphosate-based formulations, Critical Reviews in Toxicology, 43:4, 283-315. Available online from http://www.tandfonline.com/doi/full/10.3109/10408444.2013.770820#.V2G7ZtJIiUk [last accessed June, 2016]

The IARC assessed seven long term studies in rats and two studies in mice. Pancreatic islet cell adenomas were noted in male rats in two of the rat studies. However, these findings were not dose-related and/or occurred at the low dose only. The IARC also reported a statistically significant positive trend for hepatocellular adenomas in male rats only (with no evidence of pre-neoplastic lesions or progression to carcinomas), and a statistically significant positive trend for thyroid C-cell adenomas in female rats only. None of these tumours were reproduced in other chronic studies in rats.

PRVD2015-01 reported a marginal increase in the incidence of ovarian tubulostromal hyperplasia and adenomas in mice. However, since adenomas were observed at the limit dose of testing, they were not considered relevant for human health risk assessment. Furthermore, additional historical control data submitted during the PRVD comment period indicated that the incidence of ovarian adenomas was actually within the historical control range for the conducting laboratory, which increased the likelihood that these tumours were not treatment-related.

For the two mouse studies, the IARC identified a positive trend for renal tubule adenomas and carcinomas in male mice in one study, and a positive trend for hemangiosarcoma in males in the other study. However, these tumours were not reproduced in other mouse studies, which used similar and higher doses (1000-4000 mg/kg bw/day).

Since the publication of PRVD2015-01, a review by Greim et al. (2015[13]) of 14 long-term glyphosate toxicity/carcinogenicity studies in rodents included four additional studies in rats and three additional studies in mice, which were negative for carcinogenicity. These seven studies were not considered acceptable by the IARC due to insufficient reporting of the study methods and results by Greim et al. The PMRA had access to detailed information for these studies, which were considered acceptable for hazard characterization; and the USEPA and EFSA also considered these studies as part of their assessment of the carcinogenic potential of glyphosate.

2. Epidemiological Studies

The PMRA, USEPA and the European Food Safety Authority (EFSA[14]) have concluded that the currently available epidemiological database does not support a causal relationship between exposure to glyphosate and cancer outcomes.

A general discussion of pivotal epidemiology studies, as identified in the IARC assessment, is presented below.

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13 Helmut Greim, David Saltmiras, Volker Mostert & Christian Strupp, (2015), Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, Critical Reviews in Toxicology, 45:3, 185-208. Available online from http://dx.doi.org/10.3109/10408444.2014.1003423 [last accessed June, 2016]

14 Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA (European Food Safety Authority), EFSA supporting publication 2013:EN-497, 159 pp. Available online from http://www.efsa.europa.eu/en/supporting/pub/497e [Last accessed February, 2016]

Multiple Myeloma

As a part of a larger study known as the Agricultural Health Study (AHS), a prospective cohort study examined cancer incidence in pesticide applicators in Iowa and North Carolina. As described in PRVD2015-01, the most relevant finding in this study was a non-statistically significant association between multiple myeloma and glyphosate exposure. The relative risk was 1.1 when adjusted for age (95% CI, 0.5-2.4; 32 cases; only 20 cases reported exposure to glyphosate), but was 2.6 (95% CI, 0.7-9.4) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education). Evidence for an exposure-response trend by duration or intensity of pesticide use was not observed during the relatively short period (enrollment in the study was 1993-1997 to end of 2001) of follow-up (PMRA#:2391583). In a follow-up analysis of male participants in the same cohort, no correlation was observed between exposure to glyphosate and risk of a pre-malignant plasma disorder (monoclonal gammopathy of undetermined significance) that typically precedes the development of multiple myeloma (Landgren et al., 2009). In multiple re-analyses of the AHS data, including that of Sorahan (2015), no definitive association between glyphosate exposure and multiple myeloma was observed.

Non-Hodgkin lymphoma (NHL)

In many case-control studies, as reported by IARC, the USEPA and EFSA, some investigators observed a positive, but generally non-statistically significantly association between glyphosate use and NHL cases, while others reported no association. Variation in the quality of exposure assessment, study design and methods, in addition to a lack of available information on confounding variables may explain inconsistencies in the data. NHL is also not a specific disease, as mentioned by most authors of these studies, but consists of multiple types of lymphoma that are classified for convenience as not being Hodgkin's lymphoma. For example, multiple myeloma can also be considered a type of NHL; however, the data on multiple myeloma was analysed separately by the IARC, instead of considering it with NHL studies. The World Health Organization has dismissed the dichotomous classification of lymphomas as NHL/HL (Hodgkin's lymphoma); and 43 different types of lymphomas have been characterized (Berry 2010[15]). Proper classification of the disease (for example, the type of cancer) is important in epidemiology studies in order to adequately link it with the exposure to a chemical.

The interpretation of available epidemiological studies involving glyphosate is problematic due to a lack of adequate characterization of glyphosate exposures, the small number of cancer cases, and other confounding variables. For example, glyphosate exposure was analyzed with several other pesticides, exposure was generally based on questionnaires, classification of the type of cancer was not consistent, and the contribution of toxicity from formulants could not be assessed.

[15] Berry, C.L. 2010. Relativism, regulation and the dangers of indifferent science. The Sir Roy Cameron lecture of the Royal College of Pathologists. Toxicology 267 (2010) 7-13. Available online from http://www.sciencedirect.com/science/article/pii/S0300483X09005812?np=y [Last accessed February 2016]

Only once an association is plausibly established can criteria, (such as Bradford Hill) be considered to determine whether a causal relationship exists[16]. Without a causal relationship, epidemiology data cannot be used to establish references doses or occupational endpoints.

Finally, it is important to note that the experts convened by the IARC to assess the carcinogenic hazard of glyphosate concluded that there is limited evidence of glyphosate-related carcinogenicity in humans based on the available epidemiological studies. This conclusion is consistent with the limited utility of epidemiology studies in selecting reference doses to conduct a human health risk assessment for glyphosate.

While epidemiology data have inherent limitations, reported findings have the advantage of being directly based on human exposures and population responses. Because of these advantages, epidemiological studies may provide valuable information in the Adverse Outcome Pathway framework[17]. The PMRA continues to support the conduct of well-designed epidemiological studies where exposure conditions are well characterized.

Conclusion

Overall, the IARC concluded that the evidence of carcinogenicity was limited in humans but sufficient in animals. This conclusion was reached based on statistically increased incidences of tumour findings in four chronic studies in rodents (two in rats and two in mice), as well results from genotoxicity (mostly in vitro) assays using formulated products. However, the IARC did not reflect the lack of dose-response relationships or other contextual information (for example, background/ historical control data, cytotoxicity) in their decision.

Based on a weight-of-evidence analysis that utilized all available carcinogenicity studies in animals, together with other contextual information, the PMRA did not consider any of the observed tumours to be treatment-related. The main aspects of this weight-of-evidence analysis are highlighted below:

- A clear dose-response was not observed for any of the noted tumours
- The statistically significant findings via pairwise comparisons were weighed against the lack of dose-response relationships.
- The statistically significant positive trend was weighed against the lack of consistency across several relevant studies from a total of fourteen long term toxicity/carcinogenicity studies in rodents.
- Slightly increased tumour incidences at dose levels at or above the limit dose of testing (1000 mg/kg bw/day) were not considered relevant for human health risk assessment.

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16 EPA (U.S. Environmental Protection Agency), 2010, February 2010 FIFRA SAP meeting minutes: Draft Framework and Case studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment. Available online from https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0125-0079 [last accessed February, 2016]

17 OECD, Organisation for Economic Co-operation and Development (OECD), 2012, Adverse Outcome Pathways, Molecular Screening and Toxicogenomincs. Available online from http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm [Last accessed February, 2016]

- Incidences fell within valid historical control data from the respective performing laboratories.
- There was a lack of pre-neoplastic lesions (for example, foci, hypertrophy, and hyperplasia) and/or other biologically plausible evidence (for example, mode of action data) to relate the noted tumours to glyphosate treatment.
- The weight-of-evidence from a wide range of assays, both in vitro and in vivo, that examined various endpoints such as gene mutation, chromosomal damage, DNA damage and repair, indicated no genotoxic concern for glyphosate.
- The currently available epidemiology evidence does not support a causal relationship between exposure to glyphosate and cancer outcomes.

The PMRA's determination on the carcinogenic potential of glyphosate is consistent with the most recent conclusions of other international regulatory authorities and intergovernmental organizations (USEPA CARC Report,[18] EFSA,[19] JMPR,[20] ECHA,[21] and NZEPA[22]), which concluded that glyphosate is unlikely to be genotoxic or carcinogenic. Therefore, the PMRA's conclusion with respect to the carcinogenicity of glyphosate acid, as outlined in PRVD2015-01, is unchanged.

1.1.4 Immunotoxicity

Comment

The JGTF noted that no statistically significant increase in T-cell dependent antibody response or total activity in the immunotoxicity study was observed. The JGTF requested that the statement regarding "evidence of immunotoxicity" be corrected to "no evidence of immunotoxicity." The JGTF also requested that additional wording be included to qualify PMRA's conclusion of "an altered function of the immune system could not be ruled out" to provide further context to PRVD2015-01.

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18 EPA (U.S Environmental Protection Agency), 2015, Cancer Assessment Document – Evaluation of the Carcinogenic Potential of Glyphosate. Final Report. Cancer Assessment Review Committee. Available online from http://src.bna.com/eAi [Last accessed June, 2016]

19 EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015; 13(11):4302 [107 pp.] Available online from: https://www.efsa.europa.eu/en/efsajournal/pub/4302 [Last accessed June, 2016]

20 Pesticides Residues in Food, 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues – Report 2016. ISSN 2070-2515. FAO Plant Production and Protection Paper 227. Available online from http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/ [last accessed June, 2016]

21 ECHA (European Chemicals Agency). Public consultation on the harmonised classification and labelling proposal for Glyphosate. ECHA/NI/16/25. 2016. Available online from http://echa.europa.eu/view-article/-/journal_content/title/public-consultation-on-the-harmonised-classification-and-labelling-proposal-for-glyphosate [last accessed June, 2016]

22 NZEPA (New Zealand Environmental Protection Authority). Review of the Evidence Relating to Glyphosate and Carcinogenicity. 2016. Available online from http://www.epa.govt.nz/Publications/EPA_glyphosate_review.pdf [last accessed August, 2016]

PMRA Response

In the registrant-submitted immunotoxicity study, a dose-related increase in the T-cell dependent antibody response (IgM (Immunoglobulin M) AFC (Antibody Forming Cells)/10^6 spleen cells) was observed. The magnitude of increase was 10%, 18%, and 31% at 150, 449 and 1448 mg/kg bw/day, respectively, compared to the control group. The test guideline stated that a response of 800-1,000 IgM AFC/10^6 spleen cells should be noted in the negative control mice for the strain used in the AFC assay. Examination of individual animal data for T-cell dependent antibody response revealed that seven, six and eight animals in low, mid- and high dose groups, respectively, had a response higher than 1000 IgM AFC/10^6 spleen cells, compared to four animals in the control group, which indicated a treatment-related effect.

PRVD2015-01 also noted a dose-related increase in total spleen activity (IgM AFC/spleen x 10^3). The magnitude of increase for this effect was 13%, 50% and 54% @ 150, 449 and 1448 mg/kg bw/day, respectively, compared to the value of the vehicle control group. A non-dose-related increase in spleen cellularity (spleen cells $\times 10^7$) of 20% and 10% in the mid- and high dose animals, respectively was noted. This increased immune response in the AFC assay was considered potentially treatment-related. However, immune effects were not observed in the rest of the toxicity database, and ultimately, this finding did not impact the risk assessment.

In summary, the PMRA examined trends (for example, dose-response relationships) as well as statistical significance in assessing the relevance of the above findings. Given that the variation (standard deviation) in the AFC assay data are generally large, key considerations other than statistical significance were important in developing an overall conclusion. The WHO (2012[23]) recommends considering unintended immune system stimulation as a noteworthy finding, but one that may be difficult to characterize or unambiguously define as adverse. Similarly, the USFDA (2002[24]) considers unintentional immunostimulation as a potentially adverse effect.

1.1.5 Aggregate Endpoint

Comment

A number of comments contested the endpoint selected by the PMRA for aggregate risk assessment, indicating that the NOAEL of 32/34 mg/kg bw/day from a 2-year rat study was inappropriate. The comments recommended that the endpoint be based on a NOAEL of 10 mg/kg bw/day due to an increased incidence of renal tubular dilation in F_{3b} offspring at the LOAEL in a three-generation reproduction toxicity study, as identified by the USEPA Integrated Risk Information System (IRIS).

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23 WHO (World Health Organization – International Programme on Chemical Safety), 2012. Guidance for Immunotoxicity Risk Assessment for Chemicals. Available online from http://www.inchem.org/documents/harmproj/harmproj/harmproj10.pdf [Last accessed June, 2016]

24 FDA (U.S Food and Drug Administration), 2012, Guidance for Industry – Immunotoxicology Evaluation of Investigational New Drugs. Available online from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079239.pdf [last accessed June, 2016]

PMRA Response

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). An initial step in performing an aggregate risk assessment is to review all available toxicity data and to identify the most appropriate toxicological endpoints of concern and their associated parameters (such as dose, duration, and route).[25]

Since histological changes in the salivary glands were observed in many repeat-dose oral studies over various durations in two species (rats and mice), it was considered a common endpoint of concern for aggregate risk assessment (as indicated in PRVD2015-01, page 27), particularly for potential aggregate exposure from food, drinking water and residential scenarios. In addition, this was considered appropriate for all durations since the same effects were observed from very short term dosing (28-day) or chronic dosing (two-year) studies. In reconciling the dosing routes, it was indicated that dermal toxicity studies did not examine salivary glands histologically and repeat dose inhalation studies were not available. As such, effects on salivary glands are assumed to occur via inhalation or dermal routes in the absence of route-specific and convincing mode of action data to support route-specificity of these findings.

Furthermore, the reproduction study in which renal tubular dilation was noted in the F_{3b} offspring, was not considered acceptable due to many reporting limitations. It is also important to note that this finding was observed macroscopically in a few animals only, and was considered a spurious finding in the USEPA Office of Pesticides (OPP), JMPR and EFSA assessments. Additionally, this finding does not meet the criteria for determining an appropriate toxicology endpoint for aggregate risk assessment (SPN2003-04[26]). Therefore, the endpoint chosen for aggregate risk assessment in PRVD2015-01 remains unchanged.

1.1.6 Cumulative Risk Assessment

Comment

A number of submitted comments recommended that PMRA conduct an assessment of the cumulative effects of the glyphosate pest control product and other pest control products that have a common mechanism of toxicity.

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25 PMRA (Pest Management Regulatory Agency), 2003, General Principles for Performing Aggregate Exposure and Risk Assessments. Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/spn/spn2003-04-eng.pdf [Last accessed February, 2016]

26 EPA (U.S. Environmental Protection Agency), 2001, General Principles for Performing Aggregate Exposure and Risk Assessments. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf [Last accessed February, 2016]

PMRA Response

The *Pest Control Products Act* requires that PMRA assess the cumulative effects of pesticides. A cumulative assessment evaluates the potential adverse health effects from being exposed to more than one pesticide at a time from the same pesticide "group". These groups are created based on a common toxic effect that occurs by the same or similar mechanism. Glyphosate acid does not appear to share a common mode of toxicity with other pesticides. As such it does not belong to a 'pesticide group' that requires assessment of cumulative effects.

For more information and/or a description of the steps taken to determine a pesticide "group" for assessment of cumulative effects, refer to SPN2001-01.[27]

1.1.7 The *Pest Control Products Act* (PCPA) Hazard Characterization

Comment
A number of comments recommended that the PMRA apply a 10-fold *Pest Control Products Act* factor for human health risk assessment, as required under the *Pest Control Products Act*. The comments indicated that there was evidence of sensitivity of infants and children to glyphosate in the studies discussed in PRVD2015-01. In two of the three reproduction toxicity studies, decreased body weight in rat pups was noted at non-maternally toxic doses. The PMRA was also referred to studies in the published literature that reported endocrine effects and toxicity in the young.

PMRA Response

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential pre- and postnatal toxicity.

As indicated in PRVD2015-01 (page 17) with respect to the completeness of the toxicity database of glyphosate, many available guideline and non-guideline studies have investigated the potential developmental, reproductive, and endocrine effects of glyphosate. Recently, the USEPA completed an assessment of the results of their Endocrine Disrupting Screening Program (EDSP) Tier I testing and concluded that glyphosate showed no evidence of interaction with estrogen, androgen or thyroid endocrine pathways (USEPA, 2015). It is important to note that studies required in the EDSP program are of higher quality and reliability than certain studies available in the published scientific literature, including the in vitro assays cited in the comments received on PRVD2015-01.

With respect to potential pre- and postnatal toxicity, the two-generation reproduction toxicity studies in rats provided no indication of increased sensitivity of the young. In these studies, although offspring toxicity typically consisted of decreased body weight at doses that did not

[27] PMRA (Pest Management Regulatory Agency), 2001, Science Policy Notice (SPN2001-01) Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/spn/spn2001-01-eng.pdf [Last accessed June 2016]

appear to produce maternal toxicity, it was noted that these same dose levels produced toxicity in adult animals in other studies available in the glyphosate database, (PRVD2015-01, pages 14, 17, 80, 81) lessening the level of concern for this finding. Additionally, the selected reference doses provide a sufficient margin (1000-fold) to the dose levels at which the pup bodyweights were affected.

In summary, based on the completeness of the database with respect to developmental and reproductive toxicity, the10-fold *Pest Control Products Act* factor was reduced to 1-fold for most populations. However, a 3-fold *Pest Control Products Act* factor was retained for the ARfD for females 13-49 years of age, for reasons discussed in PRVD2015-01 (page 17) and Section 1.1.2 of this document. For more information on the application of the *Pest Control Products Act* factor, please refer to SPN2008-01.[28]

1.1.8 General Comments on Health Effects and Toxicology Review

Comment
A number of comments from various stakeholder organizations (for example, Canadian Association of Agri-Retailers, the Canola Council of Canada, and Central Kootenay Invasive Species Society) acknowledged and supported the proposed re-evaluation decision on the health aspects of glyphosate. These comments emphasized the importance of a science-based approach in reviewing glyphosate and agreed with the proposed regulatory label changes.

PMRA Response

The PMRA re-evaluation drew upon a large, comprehensive body of scientific information that included data from registrants, published scientific studies, as well as information from other regulatory authorities, which formed the basis of its conclusions.

1.1.9 Glyphosate, GMOs (Genetically modified) and Health effects

Comment
A number of comments cited information from various non-governmental organizations or independent researchers, and requested that the PMRA use these sources of information as evidence for health risks of pest control products containing glyphosate in order to restrict or phase-out the uses of these products in Canada.

[28] PMRA (Pest Management Regulatory Agency), 2008, Science Policy Note (SPN2008-01): The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticide. Available online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/spn2008-01/index-eng.php [Last accessed June, 2016]

PMRA Response

As noted in previous responses, the PMRA conducted a weight-of-evidence assessment that considered all relevant, hazard/toxicity data for glyphosate, including data from registrants, published scientific studies, and information from other regulatory authorities. In the PMRA assessment, published scientific toxicity data was evaluated according to the principles set out in a published USEPA guidance document.[29]

In contrast, while the documents/websites cited in these comments attempted to consolidate a wide range of sources of information, some of these studies were of low quality and reliability due to significant reporting limitations, and/or did not utilize accepted study methodologies, while others were anecdotal in nature. Also, as discussed in response to comments 1.1.3.1-1.1.3.3, studies based on formulated products are considered less relevant to characterizing the potential inherent toxicity of glyphosate itself, due to multiple and often unidentified constituents. Thus, the submitted citations did not result in a change to the toxicity assessment for glyphosate. The studies cited in these comments that were considered by the PMRA are listed in the reference list section of this document.

1.1.10 Glyphosate and Modern Diseases (such as Autism, and Celiac Disease)

Comment

A number of comments cited published articles that link glyphosate to various health problems such as autism, and celiac disease (for example, Samsel and Seneff 2013[30]; 2015[31]), and requested that PMRA restrict and/or phase-out the uses of pest control products containing glyphosate based on health effects reported in these articles.

PMRA Response

Correlations do not provide sufficient evidence of causation. These articles report disease frequencies in specific regions over several time periods. Although correlations were reported, these were difficult to interpret, as it could not be determined whether the health outcomes preceded or followed glyphosate application. These articles also lacked sufficient detail regarding the strength, consistency and specificity of the noted correlations. For example, in regions where glyphosate applications were low, it was not clear if the health outcomes occurred at lower incidences compared to those of the regions where glyphosate applications were at higher levels. Overall, due to the lack of adequate information regarding the amount, route or duration of exposure; or the timing between exposure and the onset of the symptoms, an association and/or causality relationship could not be assessed.

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29 EPA (U.S. Environmental Protection Agency), 2012, Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. Available online from http://www2.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf [last accessed February, 2016]

30 Samsel A, and Seneff S. 2013. Glyphosate's suppression of Cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: pathways to modern diseases. Entropy. 15: 1416-1463.

31 Samsel A, and Seneff S. 2015. Glyphosate, pathways to modern diseases III: Manganese, neurological diseases, and associated pathologies. Surgical Neurology International. 6 (45).

1.1.11 Health Effects on the Gastrointestinal Tract and its Microbiome

Comment
A number of comments cited published articles that report an impact of glyphosate on the human intestinal microbiome, producing gastrointestinal effects which, some propose, may ultimately affect human health. Some comments noted that glyphosate is patented as an antibiotic, and requested information on the long term effects of ingesting glyphosate, on the human gut microbiome. Overall, the comments claimed that the PMRA did not address the implications of the chelation activity and antimicrobial properties of glyphosate.

PMRA Response

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[32] [33] 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.

The reference doses established by the PMRA, and documented in PRVD2015-01, include consideration of clinical signs of toxicity on the gastrointestinal tract and are considered protective of potential effects on the gastrointestinal tract.

1.1.12 Endocrine Effects

Comment
A few comments referred the PMRA to articles that indicated glyphosate was an endocrine disruptor and requested that the PMRA use this evidence to phase-out pest control products containing glyphosate.

PMRA Response

The cited articles were generally studies that examined the effects of glyphosate formulations on a specific biochemical pathway in in vitro tests. These studies frequently did not provide test material composition.

The PMRA considered multiple lines of evidence from various toxicity studies in assessing the potential for glyphosate to affect endocrine systems. Studies conducted by the NTP, guideline two-generation reproduction toxicity studies, as well as studies conducted under the US EDSP

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[32] Shehata AA, Shrödl W, Aldin AA, Hafez HM, Kürger M. 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Current Microbiology 66(4): 350-358. Available online from http://link.springer.com/article/10.1007%2Fs00284-012-0277-2 [Last accessed June, 2016]

[33] Dietert, RR. The Microbiome in early life: self-completion and microbiota protection as health priorities. Birth Defects Research (Part B) 101: 333-340 (2014). Available online from http://onlinelibrary.wiley.com/doi/10.1002/bdrb.21116/abstract [last accessed June, 2016]

program (United States Endocrine Disruptor Screening Program), were considered. Glyphosate has not been shown to interact with any specific endocrine pathway and has no physical / chemical properties or structural similarity to other chemicals that are known to interact with the endocrine system. Finally, as noted in response to comment 1.7, the USEPA completed a weight-of-evidence assessment on results obtained from the EDSP assays and concluded that glyphosate does not interact with estrogen, androgen, or thyroid pathways and that additional Tier 2 data was not triggered.

Thus, there is no compelling evidence to suggest that glyphosate has any significant adverse effect on endocrine-related pathways. See also response to comment 2.2.7.

1.1.13 Bioaccumulation

Comment
A few comments questioned whether glyphosate could accumulate in the body over time and how glyphosate is monitored to ensure levels do not go above acceptable limits that could cause health effects.

PMRA Response

No indication of glyphosate accumulation was reported in any of the toxicity studies, as summarized in PRVD2015-01. When animals received single or repeat doses (14 days), in each case, the administered dose (AD) was excreted within 7 days post-dosing and negligible levels (under 1% of AD) remained in the examined tissues. Overall, the metabolic studies indicated poor absorption from the gut, almost complete excretion, and very minor metabolism in animals. Published regulatory reports by EFSA and the USEPA confirm these results. In summary, glyphosate is not expected to accumulate in the body over time. Refer also to response 2.2.8.

1.1.14 Use of Independent Scientific Studies

Comment
A number of comments stated that the PMRA, in its review of glyphosate, appeared to consider only "seller sponsored science". The comments referred the PMRA to a number of published studies that link glyphosate to health effects. Overall, these comments emphasized support for the use of "third party" data in assessing the health effects and making the final re-evaluation decision for glyphosate, in lieu of manufacturer-supplied data.

PMRA Response

Regulatory authorities world-wide regard studies that are performed under conditions of good laboratory practices (GLP) and according to internationally agreed upon study designs, such as the OECD test guidelines, as the most reliable, reproducible, and scientifically sound. Studies conducted according to these guidelines are of sufficient statistical power to detect effects of concern, they investigate many potential endpoints of toxicological concern, and have detailed individual animal results that enable regulatory authorities to thoroughly evaluate and interpret the data in an independent manner. Adherence to these guidelines produces studies in which regulators have a high degree of confidence.

Studies conducted by academic laboratories often have lower statistical power due to the use of fewer animals, investigate far fewer toxicological endpoints, and lack sufficient detail in their published form. These limitations prevent regulatory authorities from performing an in-depth analysis of study results.

As discussed in PRVD2015-01, the re-evaluation took into account all relevant sources of toxicity data in order to evaluate the potential health effects of glyphosate acid. This included an independent review of registrant-supplied data, which are required for the pesticide review and approval process in Canada, as well as consideration of scientific publications and information from other regulatory authorities.

For more information on the toxicology data requirements for registration of pest control products in Canada, please consult Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1 - 7 and 10[34] and/or 'OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring'.[35] Refer also to comment 2.2.9.

1.1.15 Health Effects of the Glyphosate Formulated Products

Comment

A number of comments questioned why glyphosate formulated products were not assessed for their health effects, stating that the health effects discussed in PRVD2015-01 were based on the active substance (glyphosate acid).

PMRA Response

Although the majority of mammalian toxicity studies for glyphosate were conducted using the active substance (glyphosate acid), toxicology studies that assess the acute hazard of formulated products are also examined. Individual formulated products are also used for other studies, such as in the generation of residue chemistry (field trial) data considered during the risk assessment phase. For more information on the data required for the active ingredient and formulated end use products for the registration of pest control products in Canada, please consult Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1-7 and 10.

In addition, as part of the glyphosate re-evaluation, an assessment was conducted on polyethoxylated tallow amines (POEA), which are a family of compounds often used as formulants in pest control products that function as surfactants. POEA substances (CAS no.

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34 Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1, 2, 3, 4, 5, 6, 7 and 10. Available online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/data-guide-donnees/index-eng.php [Last accessed Dec, 2016]

35 OECD (Organisation for Economic Co-operation and Development), 1997, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring – Number 1. OECD Principles on Good Laboratory Practice (as revised in 1997). Available online from http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en [Last accessed June, 2016]

61791-26-2) are included on List 4B of PMRA's list of Formulants (see REG2005-01[36] page 28). Currently, formulants are categorized into one of the five lists which rank them in descending order of concern. List 4B contains formulants are of minimal concern under specific conditions of use. For more details on the regulation of formulants in pest control products, refer to the PMRA Regulatory Directive DIR2006-02.[37]

As indicated in PRVD2015-01, the USEPA completed a human health risk assessment for phosphate ester, tallowamine, ethoxylated (ATAE), which is a subfamily of POEA. The PMRA considered the USEPA review, and reviewed the available toxicity studies that made up the USEPA assessment, including the pivotal study used in endpoint selection, which was a combined repeat-dose rat toxicity study with a reproduction/developmental toxicity screening component. As noted in the USEPA assessment, glyphosate products that contain no more that 20% POEA by weight are not of concern. Currently, all registered glyphosate products in Canada meet this limit.

1.2 Comments Related to Occupational / Residential Exposure

1.2.1 Bystanders

Comment
There were many general comments suggesting that the current level of non-dietary exposure to glyphosate is not safe for the general public (bystanders).

PMRA Response
Only those uses where human exposure to a pesticide is well below the level that cause effects in animal tests are considered acceptable for registration in Canada. This was confirmed with the re-evaluation of glyphosate

During the re-evaluation of glyphosate, it was recognized that there is potential for short-term exposure when entering treated non-cropland areas (in other words, hiking through forests or parks that have recently been treated with glyphosate). Calculated MOEs for all lifestages met the target MOE and are therefore not of concern to human health. In the interest of promoting best management practices and to minimize human exposure the following label statement is required:

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

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[36] PMRA (Pest Management Regulatory Agency), 2005. Regulatory Note: *PMRA List of Formulants*. Available online from http://publications.gc.ca/collections/Collection/H113-7-2005-1E.pdf [Last accessed February 2016]

[37] PMRA (Pest Management Regulatory Agency), 2006. Regulatory Directive: *Formulants Policy and Implementation Guidance Document*. Available online from http://www.hc-sc.gc.ca/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/dir/dir2006-02-eng.pdf [Last accessed February, 2016]

1.2.2 Restricted-Entry Interval

Comment
Comments questioned the basis for changing the "Restricted-Entry Interval" to 12 hours for commercial class products, when PRVD2015-01 states that postapplication risks are not of concern for all uses. Comments indicated that, in general, glyphosate dries on the plant very quickly and there are no residues that can be readily passed on to workers. It was recommended that the label not specify a time limit but should instead indicate that field entry is allowed once the herbicide application has dried.

PMRA Response
A restricted-entry interval (REI) is the period of time that agricultural workers, or anyone else, must not do hand labor in treated areas after a pesticide has been applied. This is to allow residues and vapours to dissipate to safe levels for work to be performed. Hand labour tasks involve substantial worker contact with treated surfaces such as plants, plant parts, or soil.

All pest control products with agricultural uses require a minimum REI of 12 hours to protect workers, and others, from potential risks that may occur from both immediate and longer-term exposures to pesticide residues, vapors, and particulates. A minimum 12-hour REI allows residues to dry and vapors to dissipate, limiting potential effects such as irritation or allergic reactions.

1.2.3 Personal Protective Equipment

Comment
It was noted that in the proposed label amendments for products containing glyphosate, as presented in Appendix XII of PRVD2015-01, there is no mention of proposed changes for protective clothing at the time of mixing and loading, application, clean-up and repair. For commercial formulations of glyphosate, the current label wording makes no requirement for use of personal protective equipment during application. The lack of proposed label changes for protective clothing is an important oversight, especially the lack of requirement for protective clothing during spraying.

PMRA Response
The exposure estimates for mixers, loaders, and applicators of glyphosate used in the agricultural exposure assessment presented in PRVD2015-01 were based on a baseline level of PPE (long pants, long sleeved shirts and chemical-resistant gloves). The calculated dermal, inhalation, and combined MOEs are greater than the target MOE for all mixing, loading, and applying activities and therefore are not of concern. As such, no additional requirements for protective clothing beyond the baseline level of PPE are needed, as the existing labels already include the appropriate PPE.

1.2.4 Application Rates in Aggregate Exposure Assessment

Comment
In PRVD2015-01, all three aggregate exposure scenarios initially assumed 2 applications with a 7 day interval at the highest rate. At that application rate, the calculated MOEs for adult and youth/children (6 to <11 years old) scenarios reached the target MOE of 100, but the MOE for

children (1 to <2 years old) for the post-application + incidental oral exposure + chronic dietary scenario did not. It was interpreted that the PMRA changed the aggregate assessment to one application of glyphosate with a seven-day time-weighted turf transferable residue average for the entire aggregate assessment for all populations. It was suggested to use the highest application rate and frequency of glyphosate use to assess the aggregate exposures, and, if safety margins (MOE) were not met, to propose meaningful and wide-ranging use restrictions to increase human health protection.

PMRA Response
When conducting the aggregate exposure assessment, 2 applications (with a 7 day interval) at the highest rate were assumed. All calculated MOEs reached the target MOE except for children (1 to <2 years old) for the post-application + incidental oral exposure + chronic dietary scenario. Therefore, dietary and non-dietary exposure refinements were required.

The dietary exposure assessment used US Tolerances or Codex MRLs for situations where these values were greater than Canadian MRLs. However, domestic production and import statistics indicated that barley, oats, and wheat consumed in Canada are almost totally produced in Canada (>99%), with <1% imported. Thus, it was considered reasonable to use Canadian MRLs for these crops as a refinement in the calculation of the chronic dietary exposure estimates for the purpose of aggregation with residential exposure only, rather than the US and Codex group tolerance of 30 ppm. The current Canadian MRLs in these cereal crops are as follows: barley (and barley flour) - 10 ppm, barley milling fractions (except flour) -15 ppm, oat (and oat flour) - 15 ppm, oat milling fractions (except flour) - 35 ppm, wheat (and wheat flour) - 5 ppm, and wheat milling fraction (except flour) - 15 ppm.

In addition, assuming 2 applications (with a 7 day interval) at the maximum application rate is a highly conservative exposure assumption, as it is unlikely that children would be exposed to turf residues of the highest rate, at the lowest interval of application immediately after application. Therefore, a refinement using 1 application of glyphosate along with a 7 day time-weighted TTR average was used (the average resides of glyphosate were calculated over a 7 day span) for the entire aggregate assessment for all populations.

These refinements are health protective and all calculated MOEs met the target MOE and are not of concern to human health.

1.3 Comments Related to Dietary Exposure

1.3.1 Genetically Modified Crops

Comment
A number of comments expressed concern regarding the potential for higher residue levels of glyphosate in genetically modified (GM) crops, as reported in the article "*Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM Soybeans. Bohn, T. et al., Food Chem. 2014, 153: 207-215.*"

PMRA Response

The residue chemistry of glyphosate, i.e. the nature and magnitude of residues of glyphosate in conventional (non-GM) crops, as well as in GM crops, is well understood and extensively documented. PMRA has received and reviewed all the metabolism studies required as per the PMRA Residue Chemistry Guidelines (Dir98-02[38]). The residue definition (RD) in plant commodities is based on scientifically sound metabolism studies conducted specifically in both types of crops. Whenever a new variant of GM crop is introduced on the market, the residue definition is reassessed based on mandatory supporting metabolism studies in that particular GM crop variant. The residue definition in animal commodities (resulting from feeding of the GM crop) is adjusted accordingly.

Currently there are three types of soybeans on the market: conventional (non-GM) soybean, EPSPS-GM soybean (containing the EPSPS gene) and GAT-GM soybean (containing the GAT gene). Based on metabolism studies in the respective crops, the RD in conventional and EPSPS soybeans are defined as the sum of glyphosate and its metabolite aminomethylphosphonic acid (AMPA). The RD in GAT soybean includes additional metabolites (acetylated glyphosate and acetylated AMPA) resulting from the specific biotransformation of glyphosate in GAT crops. As soybeans sold on the market cannot be distinguished with regards to whether they are conventional, EPSPS or GAT soybeans, the PMRA uses the most inclusive RD for soybeans, i.e., the RD in soybeans is the sum of glyphosate, AMPA and their acetylated counterparts.

All the metabolites included in the RD were deemed toxicologically equivalent to glyphosate. Consequently, in terms of residues, all the metabolites are expressed as the stoichiometric equivalent of glyphosate by using the appropriate molecular weight conversion factor (MWCF). The MWCFs are 1.5 for AMPA, 1.1 for N-acetyl AMPA and 0.8 for N-acetyl glyphosate. This means that the residue of glyphosate in soybeans (and in canola and corn comprising similar GM variants) is calculated as the sum: glyphosate + 1.5 AMPA + 1.1 N-acetyl AMPA + 0.8 N-acetyl glyphosate.

Residues of glyphosate (or any pesticide) in soybeans (or any crop) is a function of the agricultural practice by which they have been produced. GM soybeans are expected to have residue detects due to repeated spraying (in compliance with label directions) of plants throughout the production season. Conventional soybeans will contain lower residues levels because glyphosate is applied to weeds (before planting) and not on soybean plants. These facts are supported by field trial residue studies, which, as noted above, are required as per the PMRA Residue Chemistry Guidelines (Dir98-02). The field trial studies are conducted according to the petitioned-for use pattern and usage conditions (good agricultural practices) and constitute the basis for the registration and establishment of Maximum Residue Limits (MRLs). MRLs are established on the basis of worse case scenarios (maximum application rate, highest frequency of applications and shortest pre-harvest interval) within the agricultural practices. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The results presented in the cited article did not exceed the established MRL of 20 mg/kg (20 ppm) for glyphosate in soybeans and confirm that current Canadian MRLs of glyphosate (including the metabolites) in

[38] PMRA (Pest Management Regulatory Agency), 1998. Regulatory Directive: *Residue Chemistry Guidelines*. Can be requested online from http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir98-02/index-eng.php [Last accessed August 2016]

soybeans are adequate. These MRLs were used in the estimation of short term (acute) as well as long term (chronic) dietary exposures. No dietary risk concerns were identified, as the levels of exposure estimates were well below the reference doses set for dietary risk assessment (the ARfD and ADI).

1.3.2 Mitigation Measures

Comment
A question was raised regarding a general (introductory) statement in Section 3.2 of PRVD2015-01 (Dietary Exposure and Risk Assessment) which reads: "*In situations where the need to mitigate dietary exposure has been identified, the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern.*" The comment indicated that this statement implies that there are concerns with the glyphosate use pattern and, therefore, requested clarity on what mitigation measures were proposed.

PMRA Response
This is a general statement which would apply to any pesticide presenting dietary risk concerns. As no dietary risk concerns were identified for glyphosate, no mitigation measures were required.

1.3.3 Food Labelling

Comment
A comment requested that "glyphosate content" be added to all food labels (in grocery stores) so that consumers could decide whether they want to buy food containing glyphosate residues or not.

PMRA Response
Although Health Canada and the Canadian Food Inspection Agency (CFIA) share the responsibility for food labelling policies under the *Food and Drugs Act*, food labelling does not fall within the mandate of the PMRA or the *Pest Control Products Act* (PCPA). Other areas of Health Canada are responsible for developing policy and setting standards related to the health and safety aspects of labelling under the *Food and Drugs Act and Regulations*, whereas the CFIA applies these policies and enforces the regulations. The CFIA also has the mandate to develop general food labelling policies and regulations not related to health and safety. In particular, the CFIA is responsible for protecting consumers from misrepresentation and fraud with respect to food labelling, packaging and advertising, and for prescribing basic food labelling and advertising requirements.

With respect to glyphosate residues in foods, the CFIA is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada. In addition, both Canadian and international producers are aware of these MRLs and must comply with them in order to sell their produce in Canada or export to other countries that also have MRLs established. Therefore, it is expected that foods with residues higher than the MRL would not be present in the Canadian food supply.

For more details, please visit the CFIA Website at http://www.inspection.gc.ca/food/labelling/food-labelling-for-industry/method-of-production-claims/genetically-engineered-foods/eng/1333373177199/1333373638071

1.3.4 Glyphosate Used as Desiccant and Residue

Comment
Comments expressed concern about the use of glyphosate for pre-harvest desiccation on conventional crops, the level of residues left on desiccated crops at harvest and the resulting long-term dietary exposure.

PMRA Response
Glyphosate is registered for pre-harvest use (desiccation) on a number of conventional crops including wheat, barley, oats, canola, flax, lentils, peas, dry beans, and soybeans. To support this use, field trial residue studies were required to determine the level of residues resulting from the pre-harvest desiccation conducted according to the requested use pattern. Maximum residue limits (MRLs) for these crops were established on the basis of the submitted studies. Those MRLs were included in the estimation of short term (acute) as well as long term (chronic) dietary exposures. During PMRA's assessment, no dietary risk concerns were identified, as the levels of exposure estimates were well below the reference doses set for dietary risk assessment (the ARfD and ADI).

1.3.5 Safety of GMO Crops

Comment
There were general questions as to whether GM crops are safe for human consumption.

PMRA Response
Health Canada conducts a rigorous and thorough science-based assessment of all GM food products before they are allowed to enter the Canadian marketplace. The assessments are conducted under the *Food and Drug Regulations*, which prohibit manufacturers of these products from selling them in Canada until Health Canada has completed a full safety assessment and has found them to be as safe and nutritious as conventional foods.

The approach taken by Health Canada in the safety assessment of GM foods is based upon scientific principles developed through expert international consultation over the last twenty years with agencies such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Organization for Economic Co-operation and Development (OECD). This same approach is currently applied by regulatory authorities around the world in countries such as the European Union, Australia/New Zealand, Japan and the United States. For more details, please visit the Health Canada Website at http://www.hc-sc.gc.ca/fn-an/gmf-agm/index-eng.php.

1.3.6 Acceptable Level of Exposure

Comment
Comments included the question: "What is considered as acceptable level of exposure and how is that monitored to be sure that levels do not become unacceptable?"

PMRA Response
When assessing pesticide related health risks, two key factors are considered: the dose levels at which no health effects occur in animal testing (basis for the establishment of toxicological reference doses for humans) and the levels to which people may be exposed through diet, when handling and applying the pesticide, or by entering treated sites (in other words, level of exposure). The dose levels used to assess risks (in other words, toxicological reference doses) are established to protect the most sensitive human population (for example, children and nursing mothers). Only pesticide uses for which the level of exposure (through diet for example) is well below levels that cause no effects in animal testing are considered acceptable for registration.

Reference doses define levels to which an individual can be exposed to a pesticide residue over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (also known as acceptable daily intake).

The amount of pesticide to which an individual is exposed (in other words, exposure) is determined by determining the amount of pesticide that is in or on the food (in other words, residue levels) and combining that with the amount and type of foods that people eat (in other words, food consumption). Risk is then estimated by comparing the level of exposure to the reference doses described above. As previously noted, if the estimated intake is less than the reference dose, there are no dietary risks of concern.

In addition, inherent to pesticide registration is the establishment of maximum residue limits (MRLs) of the pesticide in/on foods on which the pesticide has been applied. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The MRLs are calculated from residue data obtained from field trials that are conducted using the maximum application rate and the shortest pre-harvest interval. These MRLs, or field trial residue values, are used to estimate the level of dietary exposure at the time of pesticide registration. A pesticide is registered only if the calculated level of exposure is acceptable (in other words, exposure does not exceed the toxicological reference dose). The Canadian Food Inspection Agency (CFIA) is responsible for monitoring the Canadian food supply for pesticide residues and work very closely with Health Canada (PMRA) to ensure that the foods available on the Canadian market are compliant with the MRLs. In 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having their full analysis completed by Spring 2017.

1.3.7 Monitoring of Glyphosate Residue

Comment
Several comments noted: 1) the necessity to monitor amounts of glyphosate applied on fields, especially where resistant weeds have emerged; 2) the necessity to measure glyphosate residues resulting from ordinary field applications (field trial residue data); 3) the necessity to obtain glyphosate residue data that are reflective of foods as consumed through monitoring programs in

which food samples down the chain of commerce are sampled and analysed; 4) further information on maximum residue levels of glyphosate in food; and 5) the necessity to monitor glyphosate residues in body fluids and tissues (biomonitoring); as they are not included in the *Third Report on Biomonitoring of Environmental Chemicals in Canada.*

PMRA Response

As noted in response to comment 1.3.6, glyphosate residues on foods have been measured in field trial studies that are required to register a pesticide for specific uses, as per PMRA Residue Chemistry Guidelines (Dir98-02). These field trial data were used for the establishment of maximum residue limits (MRLs) for glyphosate, that is, the maximum legally allowed amount of glyphosate residue that may remain on foods when glyphosate is used according to label directions. The MRLs are enforced by law, and, the conditions of registration must be observed in all circumstances, regardless of whether resistant weeds have emerged or not. In cases of weed resistance, a higher rate than what is currently on the labels cannot be used, as this could lead to MRL exceedance and would be in violation of the *Food and Drugs Act*. The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified MRL.

The Canadian Food Inspection Agency (CFIA) is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada. As noted in response to comment 1.3.6, in 2015, the Canadian Food Inspection Agency (CFIA) tested approximately 700 samples consisting of a variety of juice and juice blends, grains and grain products, beans, lentils, and a wide variety of fruit and vegetables. The CFIA also initiated a targeted survey of approximately 2,500 samples, looking at levels of glyphosate in bean, pea, lentil, chickpea and soy products, as well as less commonly consumed grains such as barley, buckwheat and quinoa. The results show a high degree of compliance with the MRLs established by the PMRA for glyphosate. The CFIA anticipates having the full analysis completed by spring 2017. A complete list of MRLs specified in Canada can be found on the PMRA's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, for pesticides, including glyphosate, or food commodities (http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). For details on CFIA's monitoring program, please visit the CFIA website at http://www.inspection.gc.ca/food/fresh-fruits-and-vegetables/food-safety/chemical-residues/overview/eng/1374514433922/1374514696857.

Biomonitoring is a key tool used as an indicator and quantitative measure of exposure to chemicals in the environment. Human biomonitoring data contribute to our understanding of exposure and provide information to inform the management of the health risks posed by chemicals. The Canadian Health Measures Survey (CHMS) is an ongoing national biomonitoring survey led by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada. Biomonitoring data have been reported for Cycle 1 (2007-2009), Cycle 2 (2009-2011) and Cycle 3 (2012-2013). Cycle 4 is currently underway, with data collection for this cycle having taken place from 2014 to 2015. These cycles are complementary, meaning that not all environmental chemicals (including pesticides) are included in a given cycle. For example, 55% of the chemicals measured in Cycle 2 were not included in Cycle 1 and about 31% of the chemicals measured in Cycle 3 were not included in previous cycles. Specific chemicals/pesticides are added to the list of measured chemicals in different cycles. Glyphosate, like many other pesticides, is being considered for inclusion in forthcoming cycles. For details on

the Canadian Health Measures Survey, please visit the Health Canada Website at http://www.hc-sc.gc.ca/ewh-semt/contaminants/human-humaine/chms-ecms-eng.php.

1.3.8 Glyphosate Use on Forest Vegetation and Effect on Health

Comment
One Aboriginal group provided the following comments:

I. Health Canada's glyphosate PRVD is based on dietary and occupational exposures that do not correspond with Anishinabek use of the territories for food, medicine and water;

II. Laboratory toxicological studies are based on reference values that do not conform to their own standards of risk, and do not take into account the cumulative effects of the environmental contaminants to which they are exposed;

III. They are concerned about the combined toxicity of glyphosate and the surfactants, solvents, and other additives.

PMRA Response
While the dietary risk assessment conducted by the PMRA does not directly assess the anticipated residues of glyphosate in edible forest vegetation, nor is the dietary burden to wild game specifically determined, based on assessments available, the PMRA does not expect that glyphosate residues from these foods would be of concern when ingested. This is because, in the dietary assessment that was conducted, residues in farm animal commodities were estimated and maximum residue limits (MRLs) were established by assuming the worst case scenario where the animal diet is considered to be comprised of 100% glyphosate-treated feedstuff, treated at the maximum application rate. This results in high-end residue estimates. For the same reason, residues in/on edible forest vegetation are expected to be low compared to MRLs established on conventional crops. These MRLs are established based on the worst case scenario, in other words, maximum application rate, shortest preharvest interval and maximum allowed number of applications per season. As noted in PRVD2015-01, using the above scenarios, there were no risk concerns from dietary exposure to glyphosate. The acute dietary exposure estimate (from food and drinking water) at the 95th percentile was 31% of the acute reference dose (ARfD) for females 13-49 years of age and ranged from 12% to 45% of the ARfD for all other population subgroups. The chronic dietary exposure estimate for the general population was 30% of the acceptable daily intake (ADI). Exposure estimates for population subgroups ranged from 20% of the ADI (for adults aged 50 years or older) to 70% of the ADI (for children 1-2 years old). Exposures less than 100% of the ARfD and ADI are not of concern. In the case of glyphosate, even when high-end (worst case) exposure estimates were used, no risk concerns to human health were identified.

The PMRA also conducted a health risk assessment for hikers walking through the forest immediately after application. The populations considered were adults, youths and children aged 6 to 10 years. From these estimates, no risk concerns were identified. As well, when exposures were aggregated (in other words, dietary exposure including from drinking water + non-dietary exposures as would occur from hiking in the forest), risks were also not of concern for the various population groups. Refer also to responses on environmental risk in Sections 2.2 and 2.4.

Regarding the cumulative effects of pesticides, please refer to the response to comments in Section comment 1.1.6 Cumulative Risk Assessment.

Regarding the combined toxicity of glyphosate and the surfactants, solvents and other additives, please refer to the response to comments in Section 1.1.15 Health Effects of the Glyphosate Formulated Products.

2.0 Comments Related to the Environmental Risk Assessments

2.1 Environmental Fate

2.1.1 Surficial and groundwater pollution and monitoring

Comment
Comments suggested or were concerned that glyphosate has the potential to leach to groundwater and natural areas, polluting water.

PMRA Response
In soil and water, glyphosate has been shown to break down quickly to aminomethylphosphonic acid (AMPA) through microbial processes and is considered to be non-persistent to moderately persistent. Glyphosate has low mobility in soil, giving it a low potential to contaminate groundwater systems, especially aquifers with low water hardness (Jayasumana et al. 2014). Glyphosate can enter surface waters when applied near water bodies or when carried in runoff, such as during a rain event on a steep slope. Glyphosate (without surfactant) and AMPA have comparable toxicological and ecotoxicological profiles, with both being considered to have low toxicity in general. According to the WHO (2004), the presence of glyphosate and AMPA at levels expected to be found in drinking water does not pose a risk to human health. Monitoring studies conducted throughout Canada indicate that glyphosate is rarely detected in groundwater. Although glyphosate is often detected in surface water, the concentrations detected are at relatively low levels that do not pose a risk of concern.

2.1.2 Glyphosate and AMPA persistence in soils and waters

Comment
Comments noted that glyphosate soil half-life values vary widely in terrestrial field dissipation studies in North America and that it may be more persistent than previously thought. Glyphosate may build up in soils and long-term negative effects are expected to occur. Glyphosate and AMPA are both frequently detected in soil and water in field dissipation studies from the United States (Battaglin et al. 2014).

PMRA Response
Glyphosate use per hectare in Canada is much lower compared to the US. Aquatic field studies conducted in Canada, including water monitoring studies, demonstrate glyphosate is detected less frequently and at lower concentrations than those reported in the US (Glozier et al. 2012, Hurley et al. 2012). The use of US field data for interpretation of the fate of glyphosate in Canada is challenging as the countries share only a few ecoregions, with climate and soil being different in much of the US where glyphosate is used as compared to Canada.

Terrestrial field dissipation studies
Laboratory studies conducted with glyphosate applied on different soils have DT_{50} (half-life) values ranging from 1 to 19.3 days, which classifies glyphosate as non-persistent to slightly persistent and indicates biotransformation by micro-organisms is effective.

Canadian terrestrial field dissipation studies show DT_{50} values ranging from 6 to 155 days for agricultural soils (average of less than 45 days) and from 24 to 82 days for forest soils (average of less than 55 days), similarly, in the US, DT_{50} values range from 1 to 174 days for agricultural soils (average of 41 days) and from <1 to 40.2 days for forest soils. The biotransformation of glyphosate is faster in forest ecosystems. In both environments, the compound is generally found in the upper soil horizons (0-15 cm depth) indicating overall that leaching to groundwater under field conditions is limited. The field data suggests glyphosate is non persistent to moderately persistent under field conditions and is not expected to carry over to the next year.

The wide range of dissipation rates, mainly in agricultural ecosystems, is likely a result of variation among soils, especially when considering foreign ecoregions (de Jonge et al. 2001; Vereecken, 2005, Borggaard and Gimsing, 2008, Farenhorst et al. 2009). Soil microbial activity may not always be efficient at transforming glyphosate or there may be other physical and chemical processes involved, reducing the rate of breakdown. Rapid adsorption to soil particles may play a role in preventing the transformation of glyphosate even in upper soil horizons where microbial activity is normally high and also when upper soil levels are not saturated with phosphate fertilizers (Helander et al. 2012). Preferential flow may play an important role, where root channels created by the death and decay of non-crop plants following glyphosate applications lead to the transport of glyphosate to lower soil horizons, however, leaching of glyphosate to deep soil horizons appears to be minimal.

Aquatic field dissipation studies
In general, aquatic field dissipation studies conducted in agricultural and forestry ecosystems in Canada and in the US indicate that glyphosate is non-persistent in natural waters (DT_{50} values ranging between ≤ 0.4 and 11.2 days).

Aquatic field dissipation studies conducted by Battaglin et al. (2014) and Battaglin and Koloc, (2014), show that glyphosate is readily transformed to AMPA by micro-organisms. Glyphosate was detected without AMPA in only 2.3% of samples, whereas AMPA was detected without glyphosate in 17.9% of samples. Both compounds were reported to be detected frequently in US soils and sediment, ditches and drains, precipitation, rivers, and streams, but less frequently in lakes, ponds, wetlands, soil water and groundwater. The study authors indicated that all concentrations of glyphosate measured were below the levels of concern for human and wildlife safety.

2.1.3 Runoff and aerial transport of glyphosate

Comment
Comments noted that the results of a runoff event studied in Argentina (Peruzzo et al. 2008) raise concerns about levels of glyphosate transported by runoff to aquatic environments. Glyphosate has been found in air and rain as demonstrated in a study conducted in Mississippi, USA (Chang et al. 2011, PMRA 2459642).

PMRA Response

The study of Peruzzo et al. 2008 suggests that rain events play an important role in transporting glyphosate present in the soil to stream water through runoff. In general, in the absence of mitigation measures to limit the run-off, especially when the ground is bare early in the season, this is not disputed. However, among all pesticides used in crop production in Argentina and elsewhere in the world, including Canada, glyphosate is among those that bind most strongly to soil. Despite glyphosate's high affinity for adsorption to soil particles, many studies have shown that the compound can find its way into water bodies, including studies from Italy (Screpanti et al., 2005; PMRA 2460734, Capri and Vicari, 2010; PMRA 2460735), the United States (Battaglin et al. 2005, PMRA 2423832, Scribner et al. 2007; PMRA 2460747, Newton et al. 1984; PMRA 1155371, Edwards et al. 1980; PMRA 2462226), Europe (Coupe et al. 2011; PMRA 2460748, Gregoire et al. 2010; PMRA 2462223, Siimes et al. 2006; PMRA 2462224), South America (Aparicio et al. 2013; PMRA 2462258) and Canada (Roy et al. 1989; PMRA 2460737, Struger et al. 2008; PMRA 1739313).

Many of the studies reported in the literature, including the one of Peruzzo et al. 2008, were conducted in ecoregions that are not equivalent to any Canadian ecoregions, meaning the soil and climatic conditions in study locations may not be relevant to conditions in Canada.

The amount of glyphosate applied in agricultural and forestry systems has increased since its first registration (about 40 years ago) and this is a factor in its frequent detection in surface waters and, more recently, in groundwaters of other countries outside North America (Sanchis et al. 2011, PMRA 2460750).

Examination of the factors controlling the transport of glyphosate to surface waters on a watershed scale is needed to determine which factors are important in this process and how these factors may change in importance, both spatially and temporally (Coupe et al. 2011, PMRA 2460748). The strong sorption of glyphosate to soil indicates that it expected to be poorly mobile. Recent studies on surface waters, both in Europe and in the Americas (North and South), suggest glyphosate could be transported to surface waters sorbed on soil particles. Detection in water may not only be a result of runoff, with drift, soil erosion, precipitation, and other processes having a role. In addition, the saturation of soils with phosphorus may play a role in reducing the sorption of glyphosate to soil particles, potentially increasing the amount carried in runoff.

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

Runoff events can be difficult to predict and the presence of glyphosate in water as a result of runoff or spray drift is expected. Proper application timing and runoff/spray drift mitigation measures can reduce potential impacts.

Monitoring studies conducted throughout Canada indicate that glyphosate is rarely detected in groundwater. Although glyphosate is often detected in surface water, the concentrations detected are at relatively low levels that do not pose a risk of concern.

Glyphosate in the atmosphere

Available information indicates that limited amounts of glyphosate may enter the atmosphere at the time of spray application.

Glyphosate was not reported (among 49 compounds) in air or rain along the Mississippi river valley following an air survey campaign in 1995 (Foreman et al. 2000 and Majewski et al. 2000) but was recently reported to be frequently detected in air particles and rain from three agricultural areas of the Midwestern USA (Mississippi, Iowa and Indiana) with detection frequency ranging from 60 to 100% in air and rain in 2007 (Chang et al. 2011, PMRA 2459642 and Majewski et al. 2014). Glyphosate occurred at concentrations equal to or greater than the concentrations of other high-use herbicides previously studied in the Midwest (Waite et al. 2005). Unlike many other pesticides, the presence of glyphosate in air is reported to be due either to spray drift or wind erosion, because it is not volatile according to its low vapour pressure (1.3×10^{-7} Pa), Henry's law constant (2.1×10^{-9} Pa m^3/mole or 2.07 x 1014 atm. m^3/mole) and ionic character in moist soils (binding effect). Glyphosate was not measured or detected in the Canadian atmosphere during the Canadian Pesticide Air Sampling Campaign of 2003 (Yao et al. 2006).

In most studies, the maximum concentrations of glyphosate in air and rain correspond to the period of application and ranged from <0.01 to 9.1 ng/m^3 and from <0.1 to 2.5mg/L in air and rain samples, respectively. However, during a 2007 air survey by Majewski et al. (2000 and 2014) detectable concentrations of glyphosate were collected over the entire growing season, not just in spring as in previous years (before GMO's introduction around 1995), which is reported to be consistent with how glyphosate is now used on genetically modified crops for post-emergent weed control during the growing season. According to Chang et al. (2011), it is not known what percentage of the applied glyphosate was introduced into the air in 2007, but it is estimated that an average of 97% of the glyphosate in the air is removed by a weekly rainfall ≥30 mm. Based on the physical chemistry of glyphosate and the fact that the scale of use is lower in Canada as compared with the US, especially in the corn belt, the concentration of glyphosate in air is not expected to be of concern in Canada.

2.2 Ecotoxicological reviews

2.2.1 Beneficial insects impacted by the use of glyphosate

Comment

Comments noted that glyphosate negatively affects pollinator species (especially bees) and beneficial insect populations. GMO crops resistant to glyphosate, such as rapeseed crops or other GMO crops that include an insecticidal protein (for example, Bt) may have significant concentrations of these compounds in their flower pollen and nectar during the growing season following several applications of the herbicide. Bees foraging on these flowers may then transfer the glyphosate (with or without the insecticidal protein) through contaminated nectar and pollen when they feed young bees, which may have negative impact.

PMRA Response

The re-evaluation of glyphosate included a detailed analysis of studies to determine risks glyphosate may pose to pollinators and beneficial insects.

Acute oral and acute contact exposure of honey bees, and honey bee brood to technical glyphosate and glyphosate formulations obtained from the registrant did not result in mortality in laboratory studies. All acute oral and acute contact LD_{50} values were greater than the highest concentrations tested. The results of the studies indicate that glyphosate formulations and technical glyphosate are relatively non-toxic to bees. The use of glyphosate is expected to pose a negligible acute contact and oral risk to bees.

Direct exposure of bees to glyphosate through oral and contact tests represents a conservative exposure scenario as compared to the exposure bees receive from foraging on flowering rapeseed during a very specific time during the growing season.

A honey bee brood field study (Thompson, 2012) was reviewed by EFSA, 2015. Study results were also published in 2014 (Thompson et al. 2014), where the potential for glyphosate toxicity to developing honey bee larvae and pupae (tested with the Technical IPA salt and a glyphosate formulation (MON 52276)) when fed directly to honey bee colonies, showed a NOAEL (No Observed Adverse Effect Level) for brood development of honey bee colonies of 301 mg glyphosate a.e./L sucrose solution, the highest dose tested. EFSA concluded that glyphosate formulations (with POEA and without POEA) are relatively non-toxic to bees in terms of acute contact and acute oral routes to bees and honey bee brood.

Study results of Jadhav et al. 2008 showed no direct detrimental effects of glyphosate formulation with POEA on two water hyacinth biocontrol agents, *Neochetina eichhorniae* and *N. bruchi*. Jackson and Pitre (2004) demonstrated that the Roundup Ready soybean system, including applications of glyphosate, had no detrimental effects on pest and beneficial insects (*Cerotoma trifurcate* (Forster), *Spissistilus festinus* (Say), *Hypena scabra* (F.), and *Anticarsia gemmatalis* (Hübner) in wide-row soybean plantings. Study results of Hendrix and Parmelee (1985) showed that decomposition and microarthropod densities in glyphosate-treated grass litter (*Sorghum halepense*) were higher than untreated controls. Haughton et al. (2001a and 2001b) demonstrated that glyphosate spray applications were non-toxic to non-target spiders *Lepthyphantes tenuis* but that the loss of habitat was responsible for the reduction in abundance of the species. Similar observations and conclusions were found in tests carried out on the spider *Gonatium rubens* by Haughton et al. (1999).

Results of acute and chronic laboratory studies examining the toxicity of glyphosate formulations to the springtail *Folsomia candida* indicated that glyphosate formulations were not toxic to adult springtails up to the highest concentrations tested (Santos et al. 2012, PMRA 2469288). Results of acute and chronic laboratory studies examining the toxicity of glyphosate formulations to various other beneficial terrestrial arthropods on glass plates, leaf substrate and on artificial soil substrate generally indicate that glyphosate formulations were not toxic to the predatory mite (*Euseius victoriensis*) (Bernard et al. 2010; PMRA 2462245), the lacewing (*Chrysoperla carnea*) (SERA, 2010; PMRA 2469282), the hoverfly (*Episyrphus balteatus*) (Kedwards and Travis, 2001; PMRA 1213236), the carabid beetle (*Poecilus cupreus*) (Walker et al. 2000; PMRA 1213231) or the Staphylinid beetle (*Aleochara bilineata*) (Hermann, 2001; PMRA 1213232) up to the highest concentrations tested. Based on the weight of evidence, the risk to beneficial arthropods from the use of glyphosate is not expected to be of concern.

A study conducted by Murray et al. (2009) show that 50% of all wild bee species nest in a burrow in the ground. The intensification of agriculture may be contributing to the loss of foraging habitats and nesting sites for wild bees.

Studies by Duan et al. (2008) and Malone and Burgess (2009) show no adverse effects of glyphosate resistant Bt crops on exposed bees. These results are corroborated by Morandin and Winston (2003), Malone et al. (2007) and Babendreier et al. (2008), who looked at bumblebee colony exposure to Bt.

2.2.2 The Monarch Butterfly

Comment
Comments noted that the Monarch Butterfly is at risk due to the destruction of milkweed habitat resulting from the use of glyphosate.

PMRA Response
Monarch butterflies (*Danaus plexippus*) rely completely on plants in the milkweed family, especially the common milkweed (*Asclepias syriaca*) for both reproduction and larval food. Until recently, this plant was readily found in the Midwestern Corn Belt of the US and southern latitudes of Canada.

Monarch habitat has been documented to be in decline for the last 20 years in North America (Pleasants and Oberhauser, 2012, Brower et al. 2012, Bhowmik, 1994). Before the introduction of GMO crops, glyphosate was applied in spring at the pre-emergence stage of crops and had limited impact on the survival of the common milkweed (Waldecker and Wyse, 1985, Doll 1998). But recent introduction of GMO crops resistant to glyphosate enables herbicide treatments to be done very late in the growing season (Carpenter and Gianessi, 1999 and Duke and Powles, 2008), impacting the last emerged shoots of the common milkweed, and thus, compromising its survival.

For the monarch, the decline in milkweed represents a threat since the plant is now incapable of re-colonizing fields after GMO crop harvest, especially in the corn belt of the USA and now in the low latitude fields of Canada. The discussion is open as to what the grower should do regarding the competition of the milkweed and other weeds against his own crop within a specific field and/or the protection of the milkweed within the same field.

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

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

2.2.3 Effect of glyphosate and its different formulations on soil microbes

Comment
Comments noted that PRVD 2015-01 did not address serious concerns related to glyphosate's chelation activity and antimicrobial (and antibiotic) properties. Recent published articles have reported that glyphosate and genetically modified (GM) crops can impact soil microbial populations (Fernandez et al. 2009). Glyphosate, like an antibiotic, may kill fungi in the soil, preventing soil microbes from delivering nutrients (minerals in particular) to plants and may increase plant diseases. Glyphosate may act on the shikimate pathway of gut bacteria. Research methods used in studies are not sensitive enough to properly determine the impact glyphosate has on soil microbial populations.

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

2.2.4 Birds and mammals exposed to glyphosate and its formulations containing polyethoxylated tallow amine (POEA)

Comment
Comments noted that glyphosate has negative effects on non-target animals. Studies from the United Kingdom demonstrate that glyphosate contributes to a decline in bird species and is also believed to be responsible for increased livestock diseases, such as infertility, nutrient deficiencies (connected to Mn deficiencies), stillbirths, birth defects and abnormal bone formation. Glyphosate, in combination with surfactants used in glyphosate end use products (for example, POEA), is also more toxic to non-target organisms (animals and plants) than glyphosate alone.

PMRA Response
<u>Birds</u>
As presented in the PRVD2015-01, several oral, dietary and chronic toxicity studies were conducted with glyphosate technical and formulations on the bobwhite quail, *Colinus virginianus*, and the mallard duck, *Anas platyrhynchos*. Toxicity studies were also available for the canary, *Serinus canaria* (acute oral exposure with technical glyphosate) and the chicken (21-day dietary exposure with a glyphosate formulation). Glyphosate technical was not toxic to birds

on an acute oral, dietary or reproductive basis up to the highest concentrations or doses tested (PRVD2015-01). Similarly, glyphosate formulations are not particularly toxic to birds on an acute oral and dietary basis (reproduction tests were not available with glyphosate formulations). While acute oral exposure to glyphosate formulations resulted in bird mortality at high doses, glyphosate formulations were not toxic to birds up to the highest concentrations tested when exposure occurred through the diet. There is no indication that glyphosate formulations containing the surfactant POEA are more toxic to birds than formulations without it. Endpoints and risk quotients calculated using these studies are conservative as none of the toxicity studies conducted with technical glyphosate resulted in measured toxic effects in birds.

Although bird toxicity studies indicate that acute oral exposure to high doses of wet, unaltered, glyphosate formulations can result in effects, these effects are not observed when exposure occurs from dried residues of the formulation in the diet. Exposure to glyphosate formulations through the consumption of contaminated food items is a more relevant route of exposure for the environmental assessment than acute oral exposure to the wet formulation. The time period during which wet unaltered formulated product would be present on food items is very limited. Exposure is likely to be mostly from ingestion of dried residues on food items. It is noted that exposure via preening, which may be a relevant exposure route for wet formulation, is not considered in the current assessments. Thus, more weight is given to conclusions of the dietary assessment than to the acute oral assessment. The risk to birds from acute oral, dietary and reproduction exposure to glyphosate and its formulations is expected to be low.

One comment also reported the study of Newton (2004) as evidence of major farmland bird declines in the UK in connection with herbicide uses (not specifically glyphosate) and agricultural practices that would be responsible for the reduction of habitat and/or food available to many species.

Other studies indicate minimal impacts or even the absence of negative impacts on bird community structure and densities following glyphosate treatments in forests and vegetative changes after clearcuts (Morrison and Meslow, 1984; Mackinnon and Freedman, 1993). Other studies (Linz et al. 1992, Linz et al. 1994, Linz et al.1995, Linz et al. 1996a, Linz et al. 1996b, and Solberg and Higgins, 1993) show that glyphosate treatment in wetlands to control invasive species such as cattails (*Typha* spp.) was efficient and had positive impacts by restoring bird habitats (open water) and by increasing original population and diversity.

A review by Sullivan and Sullivan (2003; PMRA 2469318) reported that species richness and diversity of songbirds and small mammals were little affected by glyphosate-induced habitat alteration. Some species declined rapidly following treatment, whereas others increased in abundance. The effect of glyphosate on large mammalian herbivores was measured by the abundance of animals and food plants and by habitat use. Hares and deer were little affected, whereas reductions in plant biomass and related moose forage and habitat use generally occurred for the first few years after treatment, but not thereafter.

Studies in North America have identified habitat loss as the major cause of bird declines over the last 25 years (Santillo et al. 1989 and Hardy and Desgranges, 1990).

Mammals
Numerous acute oral toxicity studies on mammals were available for glyphosate technical and various glyphosate formulations. There is no indication that formulations containing the surfactant POEA are more toxic to mammals than formulations without POEA. Six multi-generation reproduction studies with exposure through the diet were available for technical glyphosate. No reproduction studies with glyphosate formulations were available.

Most mammalian toxicity studies show that exposure to high levels of glyphosate technical or its formulations does not result in toxic effects on mammals. Based on 60 acute oral studies, toxic effects were observed at high doses only in three studies conducted with glyphosate technical, and eight studies with glyphosate formulations. The majority of the available data indicate that risks to mammals following acute oral exposure to glyphosate and its formulations are low. Acute risks to mammals would be restricted to on-field exposure of only a few guilds (herbivores and insectivores). No reproductive risks to mammals are expected from the use of glyphosate. In addition, there are no incident reports for mammals related to the use of glyphosate.

2.2.5 Risk to Amphibians

Comment
Comments noted that glyphosate contributes to the decline of frog abundance. Glyphosate alone (Paganelli et al. 2010), and in combination with POEA, poses risks to amphibians according to studies of Relyea (2005a, 2005b and 2005c) and review of Annett et al. 2014.

PMRA Response
Toxicity data were available for 32 species of amphibians at various stages of development. As is shown with invertebrates and fish, the toxicity of technical glyphosate and its salts and glyphosate formulations containing non-POEA surfactants to amphibians is relatively low (acute LC_{50} = >17.9–7297 mg a.e./L) compared with glyphosate formulations containing POEA (acute LC_{50} = 0.8–51.8 mg a.e./L). Similarly, the results from subchronic and chronic laboratory studies and outdoor mesocosm studies with amphibians demonstrate that exposure to glyphosate formulations containing POEA elicit lethal and sublethal effects (for example, reduced body size, abnormal development, decreased time to metamorphosis) at relatively low concentrations (LC_{50} = 1.0–22.8 mg a.e./L, NOEC = 0.006 - >1.8 mg a.e./L).

Although acute studies showed no negative impacts on amphibians from glyphosate TGAI and formulations that do not contain POEA, a refined risk assessment conducted on amphibians (including frogs) exposed to glyphosate formulations containing POEA (lab tests) indicated that the level of concern was slightly exceeded (RQ = 1.1-1.2) for end-use products containing the surfactant POEA and tested in lab. Level of concern was not exceeded for refined mesocosm studies. Relyea (2005a and b) demonstrated a glyphosate formulation containing the surfactant POEA was responsible for the kill of 68-86% of juvenile amphibians exposed. This study, along with other amphibian studies, was considered in the re-evaluation of glyphosate and used to determine an HC_5 endpoint value from an SSD analysis. Results revealed an acute and chronic HC_5 of 0.93 and 0.86 mg a.e./L, respectively for glyphosate formulations containing the POEA surfactant that were used in the refined risk assessment. As a result, mitigation measures, in the form of no spray buffer zones, are identified on product labels and are required to protect amphibians. Risks to amphibians are not of concern if labelled spray buffer zone requirements are followed.

Annett et al. (2014), in their review, report the mode of action of different glyphosate formulations and their potential negative impact related to the inhibition of the enzyme acetylcholisesterase of some aquatic species as well as the oxidative stress due to Reactive Oxygen Species (ROS) causing damage to nucleic acid, lipids and proteins in aquatic species such as amphibian and fish that can lead to cell death. Studies reviewed, and reported by Annett et al. (2014) were also reviewed by the PMRA, with many of the reported endpoints being used by the PMRA in the risk assessment of glyphosate.

While there is evidence from laboratory studies suggesting that glyphosate products containing POEA are more toxic to amphibians than glyphosate alone, when considered in the context of all the studies available, particularly field studies conducted under actual use conditions, there is no compelling or credible evidence that gives rise to a serious possibility that glyphosate products containing POEA may cause an unacceptable environmental risk. In addition, while lower tier studies conducted in a laboratory showed potential for effects, a field study conducted under operational conditions (Thompson et al. 2004, PMRA 2032071) showed no significant adverse effects on amphibians. Moreover, glyphosate products containing POEA are used in forestry to prepare the site for reforestation which requires that the products be applied only once per silviculture cycle; typically equating to once every 50 to 80 years. As such, the potential for amphibian exposure to glyphosate products is limited in silviculture. Based on these findings, the PMRA concluded that there were no reasonable grounds to believe that the environmental risk to amphibians in small ephemeral forest wetlands from the spraying of glyphosate products was unacceptable.

2.2.6 Other Aquatic organisms

Comment

Comments noted that the following studies were not taken into account in the re-evaluation of glyphosate: Vera et al. 2010 (periphyton), Fairchild et al. 2002 (Atlantic salmon), and Sihtmae et al. 2013 (aquatic invertebrates).

PMRA Response

Periphyton

The study of Vera et al. 2010 entitled ''New evidence of Roundup impact on the aquatic periphyton community and the quality of freshwater ecosystems'' (Ecotoxicology 19:710-721) was in fact considered qualitatively in the re-evaluation, but no endpoints were available in the study to be used as part of the SSD analysis. The study of Bonnineau et al. 2012 (PMRA# 2462244) on periphyton was preferred and the freshwater algae acute 6hr-EC_{50} endpoint of 8.7 mg a.e./L was used in the re-evaluation of glyphosate and presented in PRVD2015-01.

Atlantic salmon

The study of Fairchild et al. 2002, entitled "Effects of freshwater contaminants on marine survival in Atlantic salmon" (NPAFC Tech Report No. 4) was examined and it was determined that the study is related to the active atrazine and does not report on glyphosate.

Aquatic invertebrates
The study of Sihtmae et al. 2013 entitled "Ecotoxicological effects of different glyphosate formulations'' (Applied Soil Ecology 72:215-224) was indeed used in the re-evaluation of glyphopsate. The freshwater invertebrate endpoint values reported by Sihtmae et al. 2013 (PMRA 2574468) were used in the determination of HC_5 values from a SSD analysis. Refer to response 2.3.2 below.

2.2.7 Endocrine disruption

Comment
Comments noted that the PMRA should phase out the use of products containing glyphosate based on articles that have identified glyphosate as an endocrine disruptor.

PMRA Response
The USEPA's Endocrine Disruptor Screening Program (EDSP) is currently working to validate the assays proposed by the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), many of which are being validated in coordination with the OECD through the Endocrine Disrupters Testing and Assessment (EDTA) and the Validation Management Groups (VMGs). The results of screening tests for glyphosate are available on the following website: (http://www2.epa.gov/sites/production/files/2015-06/documents/glyphosate-417300_2015-06-29_txr0057175.pdf).

Although the study by Antoniou et al. 2012 raised concerns regarding the potential impact of glyphosate as an endocrine disruptor, the conclusion is that glyphosate demonstrates no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways in mammals or wildlife. Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for glyphosate. Also refer to response to comment 1.1.12.

2.2.8 Bioaccumulation

Comment
Comments questioned if glyphosate can accumulate in the body over time and how levels of glyphosate are monitored to ensure that it does not go above acceptable limits that could cause detrimental health effects to animals?

PMRA Response
Information available on the bioaccumulation potential of glyphosate is presented in the PRVD 2015-01. Glyphosate is not expected to bioaccumulate due to its high polarity (log K_{ow} = -2.8 to -0.67) and anionic character (Mensink and Janseen, 1994, PMRA 2462253 and Villeneuve, J., 2012 (PMRA 2203372)). A maximum bioconcentration factor (BCF) of 1.6 was reported for bluegill sunfish exposed to 0.6 mg/L for 28 days (Wang et al. 1994b; PMRA 2460743 and Takacs et al. 2002; PMRA 2462252). BCF values of 12 to 35.4 and 10 to 42.3 for tilapia and carp, respectively were also reported by Wang et al. 1994b (PMRA 2460743). Channel catfish, largemouth bass and rainbow trout exposed to 10 mg/L glyphosate for 14 d had BAFs of 0.18, 0.04, and 0.03, respectively (Kramer and Beasley, 1975, PMRA 1182548).

2.2.9 Science based approach and the use of independent scientific studies in the environmental risk assessment.

Comment
Various stakeholder organizations emphasized the importance of a science-based approach and agreed with the proposed regulatory label changes. Other commenters encouraged to use a number of different sources of information that claim glyphosate poses an environmental risk. Sources of information from various non-governmental organizations or independent researchers were provided. In addition to registrant submitted studies, work done by third parties (independent research) should be used in assessing the environmental effects of glyphosate and in making the final re-evaluation decision.

Some commenters believe that the environmental risk assessment for glyphosate was conducted using only studies provided by the registrants and that there has not been enough long-term testing of glyphosate done by independent scientists. Reviewing studies conducted and provided by the company that is seeking registration of the product is perceived as a conflict of interest and highly biased as these studies are not peer reviewed by the scientific community. Reference was provided to a number of published scientific studies that link glyphosate to environmental and agronomic effects.

PMRA Response
The environmental risk assessment of glyphosate was conducted using a science-based approach and included consideration of a large volume of literature. In addition to registrant supplied data, more than 1500 scientific articles related to glyphosate were examined, with approximately 250 of these studies being deemed relevant and useful for consideration in the environmental risk assessment. Values obtained from the public literature were used in combination with the registrant data set in order to strengthen the environmental risk assessment. Due to the tremendous amount of endpoint data available for different aquatic and terrestrial organisms, SSD analysis was employed to determine HC_5 and HD_5 values that were used in the risk assessment. Also refer to response to comment 1.1.14.

2.2.10 Assessment of formulations

Comment
Commenters questioned why the formulations of glyphosate products are not assessed for their environmental effects. Environmental effects discussed in the PRVD2015-01 were based primarily on the active substance (in other words, glyphosate).

PMRA Response
PRVD2015-01 includes risk assessments for not only the technical active ingredient, but also the various formulations, including those that contain POEA. Endpoints using values from EUPs were used to derive HD_5/HC_5 values from SSD calculations when possible. The risk assessment includes a comparison of the exposure of terrestrial and aquatic organisms to technical glyphosate and the formulations.

2.3 Risk assessment and methodology

2.3.1 Endpoint selection

Comment
Some endpoints used in the terrestrial and aquatic plant risk assessment as well as the risk assessment for aquatic organisms were inappropriate. The quality of some of the data used in the risk assessment was not clear and was questionable. Specific studies that were at issue were identified for the PMRA to reconsider. The process used to review and ensure the quality of open literature studies used in the risk assessment needs to be more transparent.

PMRA Response
Endpoints derived from unpublished registrant/applicant submitted data follow guidelines set by regulatory bodies and are subject to good laboratory practice standards. These studies have clear objectives, scientific and analytical protocols, and the data has been subject to appropriate statistical analysis. On the other hand, published scientific papers are written in a concise way in order to bring enough information and details for the reader to accept or reject the conclusion of the author(s). Although published scientific articles are subject to a scientific peer review that strengthens their validity, information in published studies must have sufficient detail so that the scientific methods (protocol) and the results obtained are reproducable. Unfortunately, many published scientific studies lack sufficient detail, reducing confidence in the conclusion reached by the author(s). As a result, some published scientific papers are rejected when reviewed by the PMRA during the re-evaluation process. (Refer also to response to comment 1.1.14).

That said, as a result of comments received during the comment period for the PRVD2015-01, endpoints questioned in the comments have been re-examined and changes to the risk assessment have been made based on a revised assessment of their validity. References associated with endpoint values are presented in the tables found in (Appendix III).

2.3.2 SSD model

Comment
The methodology for deriving Species Sensitivity Distributions (SSDs) is not fully described in the PRVD and the requirements for inclusion of endpoints is not discussed. The use of a combination of terrestrial plant EC_{25} and EC_{50} endpoints for vegetative vigour in SSD calculations should be reconsidered.

PMRA Response
The toxicity data analysis includes the determination of HC_5 or HD_5 values using an SSD or species sensitivity distribution. An SSD is a plot of all species' toxicity endpoints within a taxonomic group against a cumulative density function. An SSD is determined by fitting a theoretical distribution to the data set, such as a log-normal distribution, and allows the derivation of community level threshold concentrations such as the HC_5. The hazardous concentration (HC_5) or dose (HD_5) to five percent of species is calculated for acute and chronic data sets separately, using the acute LC_{50}/EC_{50} values and chronic NOEC/NOEL values, respectively. An SSD is constructed for acute and chronic effects for every taxonomic group where sufficient toxicity data are available. Acute toxicity data generally refers to short term studies, with the endpoints (LC_X or EC_x) being derived from effects on survival or other

endpoints considered to affect survival. Chronic and sub-chronic studies generally aim to determine sublethal effects and the associated NOEC or NOEL concentration. Different endpoints can also be used in SSDs such as the EC_{25} for terrestrial plants or other EC_X value such as an $EC_5/_{10}$ may be considered relevant and appropriate to the assessment. If SSDs cannot be calculated, the most sensitive endpoints with an appropriate uncertainty factor are used in risk assessment.

The software program ETX 2.1 is used with the log-normal model to generate SSDs where sufficient toxicity endpoints are available for different taxonomic groups. The median HC_5 values are reported for SSDs. The variability in the data sets is indicated not only by the upper and lower bound HC_5 estimates but also the confidence limit of the fraction of species affected (FA), which indicates the theoretical minimum and maximum percent of species that could be affected based on the available data when the population is exposed to the HC_5 concentration.

SSDs were determined for glyphosate herbicide for the following taxonomic groups (results are reported in Appendix III Tables 1 to 3):

- Freshwater organisms: invertebrates, fish, algae, amphibians, aquatic plants
- Marine organisms: fish, invertebrates and algae
- Terrestrial organisms: plants (crop and non-crop)

Where an HC_5 value cannot be determined due to insufficient species data or lack of model fit, etc., the most sensitive species endpoint is reported in summary tables without the use of uncertainty factors. Where multiple data points are available for one species, a geometric mean value is used to represent the species' sensitivity. The treatment of toxicity data is such that it allows quantitative comparisons and predictions including consistency of exposure concentration units, ecological relevance and comparability of measurement endpoints, and types of test chemicals, or duration of exposure.

All data sets were grouped by test material type including technical grade active ingredient (TGAI, includes all forms of glyphosate actives), end-use products containing the surfactant POEA (EUP + POEA), end-use products which do not contain POEA (EUP NO POEA), POEA alone and the glyphosate transformation product AMPA. All toxicity values were normalised to acid equivalent (a.e.).

Results of SSD analysis:
Glyphosate shows equal toxicity to many aquatic taxonomic groups, both acutely and chronically. The most acutely sensitive aquatic taxonomic groups are freshwater plant (overspray on aquatic macrophyte; Er_{50} of 38 g a.e/ha), freshwater and marine invertebrates, and freshwater algae (HC_5 = 0.1mg a.e./L). The lowest chronic toxicity threshold values were determined for freshwater and marine fish (NOEC = 0.28 and 0.1 mg a.e./L, respectively) and freshwater plants (chronic EC_{50} = 0.11 mg a.e./L). The most sensitive terrestrial plant endpoint for crops and non-crops is the HD_5 of EC_{50} value of 0.0658 kg a.e./ha for EUPs that contain, or do not contain POEA, based on plant vegetative vigor endpoints.

As observed for amphibian in previous section 2.2.5, it is noted that the formulated products of glyphosate are generally more toxic to some organisms than the active ingredient, as in the case of freshwater invertebrates which are two orders of magnitude (100x) more sensitive to formulations containing POEA vs. the active ingredient. Freshwater fish and plants are also more sensitive to EUPs. Marine fish on the other hand are most sensitive, on an acute basis, to the parent chemical.

Therefore the SSD analysis results indicate that the most sensitive population level aquatic toxicity threshold value (HC_5) is 0.1 mg a.e./L, based on acute and chronic endpoints for several taxanomic groups including freshwater and marine invertebrates, aquatic plants (except overspray), algae and fish. While the most sensitive population level terrestrial toxicity threshold value (HD_5 of EC_{50}) is 0.0658 mg Kg a.e./ha, based on acute toxicity to plants (crops + non-crops exposed to glyphosate formulations containing POEA + glyphosate formulations without POEA).

2.3.3 Buffer zone calculations

Comment
Comments noted that the buffer zone sizes should be recalculated based on reconsideration of acceptability of endpoints. Buffer zone sizes should be set based on scientific evidence and valid endpoints and no increase should be implemented if no such evidence exists. Please explain why buffer zones are different for treated areas of more than 500 ha and those that are less than 500 ha.

PMRA Response
The PMRA agrees with the fact that buffer zone sizes should be set based on scientific evidence and valid endpoints and no increase or decrease should be implemented if no such evidence exists. The methodology used by the PMRA to calculated buffer zones is based on scientific evidence and valid endpoints.

Endpoints were reconsidered following identification of questionable studies, which lead to changes in the endpoints included in the SSDs and the determination of HC_5 values, especially for aquatic organisms. Buffer zones have been recalculated as a result of the changes in the SSD calculations.

The reason why buffer zones are different for treated areas of more than 500 ha and those that are less than 500 ha. is the following:

The AGDISP software model (version 8.21) used by the PMRA to calculate aerial buffer zones takes into account the cumulative downwind drift associated with the number of flightlines made over a treated surface area with an aircraft. A forest surface area of more than 500 ha is considered as 'woodland' and is modelled using 50 flightlines as a realistic scenario. A forest surface area of less than 500 ha is considered as 'woodlot' and requires only 10 flightlines. As such, cumulative drift may be more significant in woodlands than in woodlots and consequently buffer zones may be larger in woodlands than in woodlots. Updated buffer zone tables are reported in Appendix IV, Tables 1 and 2.

2.4 Aerial spraying of forests

Comment
One Aboriginal group commented that aerial spraying of forests with glyphosate impacts the environment.

PMRA Response
As noted in response to comment 2.2.5, glyphosate is used for forest site preparation and plant release (conifers and deciduous trees) after trees are harvest. This use is expected to occur once every 50-80 years. As such, glyphosate exposure to forest is extremely low. In addition, glyphosate does not persist in the terrestrial environment, with DT50s ranging from 24 to 82 days in forest soils (average of less than 55 days).

For the protection of aquatic habitats, no spray buffer zones of 1 to 10 meters are required when glyphosate formulations that contain POEA are applied for forest site preparation and plant release by air. A buffer zone is defined as the distance between the point of direct pesticide application and the nearest downwind boundary of a sensitive habitat. Glyphosate does not persist in water (DT50s range from 0.4–11.2 days).

3.0 Comments Related to the Value Considerations

3.1 Glyphosate has value in contributing to Canadian agriculture and non-agricultural land management

Summary of Comments

- glyphosate is an important and cost effective weed management tool in crop production in that it can be applied at varying points of the cropping cycle from preplant to post-harvest.
- the application of glyphosate prior to harvest is important in terms of advancing the maturity and/or uniformly desiccating the crop and to control late season weeds that can interfere with harvesting operations and reduce crop quality.
- glyphosate with its unique mode of action remains an important tool for broad spectrum weed control, including of perennial, invasive and noxious weeds
- it allows the Canadian agricultural sector to remain competitive with those of its trading partners
- it remains an important tool for advancing conservation tillage, such as no-tillage and reduced tillage systems, that reduce soil erosion and increase soil organic matter
- it is used to control invasive plants to foster biodiversity by allowing native plant communities including those containing endangered or rare species, to be preserved or re-established.

PMRA Response
As stated in the PRVD2015-01, the PMRA acknowledges that glyphosate plays an important role in weed management in both Canadian agriculture and non-agricultural land management

3.2 Glyphosate has no value considering the risks to the environment and human health.

PMRA Response
The value of glyphosate to Canadian agriculture and non-agricultural land management is a result of this product's unique mode of action, diverse use pattern, and broad spectrum of weed control. As indicated in PRVD2015-01, based on a review of the science, the PMRA has concluded that this product is unlikely to affect human health or pose an unacceptable risk to the environment when used in accordance with label directions.

4.0 Other Comments Related to the Use of Glyphosate

4.1 Weed resistance

Comment
Comments noted that repeated use of glyphosate and heavy reliance on glyphosate to control weeds in today's agriculture practices increase weed resistance. PMRA has not addressed the issue of weed resistance in its re-evaluation of glyphosate. There is no mention of glyphosate-resistant weeds anywhere in the Environmental Considerations of the PMRA's Proposed Re-evaluation decision for glyphosate. A report recently published by the Canadian Biotechnology Action Network (CBAN) reveals that "there are five species of glyphosate-resistant weeds now found in Canada". An online survey of farmers from 2013 estimated that more than one million acres of Canadian farmland had glyphosate resistant weeds.

PMRA Response
The PMRA is aware of the fact that the current 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 are increasingly becoming challenge to the agricultural production system. In order to prevent or delay the development of glyphosate-resistant weeds, it is crucial to maintain diversity in weed management practices. From the regulatory perspective, the PMRA developed the resistance-management labelling program in 1999 with an aim to mitigate the risks for resistance development. Participation in this program is on a voluntary basis, but registrants are encouraged to add the resistance-management grouping symbols and resistance management statements to both new and existing product labels (Regulatory Directive DIR2013-04, *Pesticide Resistance Management Labelling Based on Target Site/Mode of Action)*. To date, the majority (about 95%) of labels for products containing glyphosate comply with the resistance-management labelling. Other organizations are more closely involved with improvements to agricultural practices.

4.2 Invasive species

Comment
Comments noted that herbicide treatments such as glyphosate are needed to control invasive species in standing water, such as *Phragmites australis* (2015 Resolution of the Canadian Federation of Agriculture Annual General Meeting).

PMRA Response
Before a pesticide is approved for use in Canada, it must undergo a thorough pre-market science-based risk assessment and meet strict health and environmental standards, and the product must have value. The use of glyphosate to control invasive species in standing water was not registered in Canada, and therefore was not considered during the re-evaluation.

The PMRA is aware of the rise of *Phragmites* in Canadian wetlands, and has been working with provincial partners to find solutions such as emergency registration where needed. An emergency use will be considered only if the product is efficacious and risks deemed acceptable.

4.3 Treaty rights and the duty to consult First Nations

Comment

One Aboriginal group commented that aerial spraying on traditional lands is a violation of treaty rights and it is a constitutional obligation for Health Canada to consult. The PMRA is obligated to hear oral testimony in their territory as a form of evidence.

PMRA Response

Concerns expressed by the aboriginal group in their written submission and in subsequent conversations, were identified as being related more to forest management practices and not specific to the use of this particular herbicide.

Following harvest, Canadian forests are either allowed to regenerate naturally or are re-planted with a crop tree species as part of a forest management plan. Glyphosate, or other herbicides, can be applied in a managed forest to control naturally occurring vegetation that could out compete newly planted crop tree seedling (for example, pine or spruce trees) for nutrients, light and space. Herbicides are also used in clearing logging roads and rights of way. As with other land management uses of pesticides such as agriculture, the use of herbicides in forestry operations can reduce biodiversity (for example, loss of grasses, raspberry and non-crop tree species, such as birch or aspen) in the application areas for a period of time.

Except on federal lands, the management of natural resources, such as forests, is the responsibility of provincial governments. Provincial ministries of natural resources are better informed about the local conditions and are generally responsible for approving sustainable forest-management plans. These plans indicate which land will be allowed to regenerate naturally and which will be re-planted and managed (with or without herbicides). If a herbicide is to be used, it must a product that is authorized by Health Canada's Pest management Regulatory Agency for forestry application. It the product is to be applied by air, permits are required, generally from provincial ministries of the environment, prior to application. Consultations with the aboriginal community on herbicide use in forestry can be most effectively done by considering forest management plans and the local land use requirements. It is recommended that the group continue to raise their concerns with the appropriate provincial authorities

Other concerns that were raised by this group regarding the impact of glyphosate use on human health and the environment were addressed under responses 1.3.8 and 2.4.

Appendix II Registered Products Containing Glyphosate in Canada as of 16 September 2016

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	29219	GLYPHOGAN PLUS LIQUID HERBICIDE	GPI-356;	SN-SOLUTION	C+R
ALBAUGH LLC	28322	CLEAROUT 41 PLUS HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C
	31913	GLYPHOSATE 480	GPI-480;	SN-SOLUTION	C
ALLIGARE, LLC	30093	ALLIGARE GLYPHOSATE 4+	GPI-360;	SN-SOLUTION	C
AGROMARKETING CO. INC.	30721	NASA 36	GPI-360;	SN-SOLUTION	C+R
AGRI STAR CANADA ULC.*	29995	CRUSH'R PLUS	GPI-360;	SN-SOLUTION	C
	32181	CRUSH'R 480	GPI-480;	SN-SOLUTION	C
	31655	AGRI STAR CRUSHR 540	GPP-540;	SN-SOLUTION	C
DOW AGROSCIENCES CANADA INC.	30958	ENLIST DUO HERBICIDE	GPX-204; DXJ-194;	SN-SOLUTION	C
	30960	GF-2726 TSOY HERBICIDE	GPX-204; DXJ-194;	SN-SOLUTION	C
	27394	PREPASS B HERBICIDE (A COMPONENT OF PREPASS HERBICIDE)	GPI-360;	SN-SOLUTION	C
	27615	VANTAGE PLUS MAX HERBICIDE SOLUTION	GPI-480;	SN-SOLUTION	C
	28245	MAVERICK II HERBICIDE SOLUTION	GPI-480;	SN-SOLUTION	C
	28540	ECLIPSE II B HERBICIDE	GPI-480;	SN-SOLUTION	C
	28977	MAVERICK III HERBICIDE	GPX-480;	SN-SOLUTION	C
	29033	ECLIPSE III B HERBICIDE	GPX-480;	SN-SOLUTION	C
	29652	PREPASS XC B HERBICIDE (A COMPONENT OF PREPASS XC HERBICIDE)	GPX-480;	SN-SOLUTION	C
	29994	VANTAGE XRT HERBICIDE	GPX-480;	SN-SOLUTION	C
	26171	VANTAGE PLUS HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C+R
	26172	VANTAGE HERBICIDE SOLUTION	GPI-356;	SN-SOLUTION	C+R
	26884	VANTAGE FORESTRY HERBICIDE	GPI-356;	SN-SOLUTION	C+R
	29588	GF-772 HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	29773	DEPOSE HERBICIDE SOLUTION	GPI-356;	SN-SOLUTION	C+R
	30516	VANTAGE MAX HERBICIDE	GPS-480;	SN-SOLUTION	C+R
	28840	VP480 HERBICIDE	GPX-480;	SN-SOLUTION	C+R
	29774	DURANGO HERBICIDE	GPX-480;	SN-SOLUTION	C+R
	30423	PREPASS 480	GPX-480;	SN-SOLUTION	C+R

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		HERBICIDE			
	32314	GF-2018 HERBICIDE	GPX-480;	SN-SOLUTION	C+R
EZJECT, INC.	21262	DIAMONDBACK HERBICIDE SHELLS	GPI-0.15;	PA-PASTE	C
FMC CORPORATION	27287	GLYFOS AU SOLUBLE CONCENTRATE HERBICIDE	GPI-360;	SN-SOLUTION	C
	28925	CHEMINOVA GLYPHOSATE (TM) II	GPI-356;	SN-SOLUTION	C
	29363	GLYFOS BIO HERBICIDE	GPI-360;	SN-SOLUTION	C
	29364	GLYFOS BIO 450 HERBICIDE	GPI-450;	SN-SOLUTION	C
	30234	FORZA BIO SILVICULTURAL HERBICIDE	GPI-360;	SN-SOLUTION	C
	30235	FORZA BIO 450 SILVICULTURAL HERBICIDE	GPI-450;	SN-SOLUTION	C
	24359	GLYFOS SOLUBLE CONCENTRATE HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	26401	FORZA SILVICULTURAL HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	28924	GLYFOS SOLUBLE CONCENTRATE HERBICIDE II	GPI-360;	SN-SOLUTION	C+R
INTERPROVINCIAL COOPERATIVE LIMITED	26846	GLYPHOSATE HERBICIDE - AGRICULTURAL & INDUSTRIAL	GPI-360;	SN-SOLUTION	C
	29216	GLYPHOSATE WATER SOLUBLE HERBICIDE	GPI-309(+51);	SN-SOLUTION	C
	27988	IPCO FACTOR 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	31199	FORTRAN 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	31598	CO-OP VECTOR 540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	29775	MATRIX HERBICIDE SOLUTION	GPX-480;	SN-SOLUTION	C+R
	30319	VECTOR HERBICIDE SOLUTION	GPX-480;	SN-SOLUTION	C+R
	31090	RIVET HERBICIDE	GPX-480;	SN-SOLUTION	C+R
JOINT GLYPHOSATE TASK FORCE, LLC	30678	JGTF GLYPHOSATE HERBICIDE	GPI-360;	SN-SOLUTION	C+R
LOVELAND PRODUCTS CANADA INC.	30076	MAD DOG PLUS	GPI-360;	SN-SOLUTION	C+R
MEY CANADA CORPORATION	29126	WISE UP HERBICIDE SOLUTION	GPI-360;	SN-SOLUTION	C
MONSANTO CANADA INC.	20423	MOCAN 943 WATER SOLUBLE HERBICIDE	GPI-120; DIC-86;	SN-SOLUTION	C
	21572	RUSTLER FALLOW LIQUID HERBICIDE	GPI-132; DIC-60;	SN-SOLUTION	C
	27200	RUSTLER LIQUID HERBICIDE	GPI-194; DIC-46;	SN-SOLUTION	C

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	32274	ROUNDUP XTEND WITH VAPORGRIP TECHNOLOGY HERBICIDE	GPI-240; DIC-120;	SN-SOLUTION	C
	19536	RUSTLER SUMMERFALLOW HERBICIDE	GPI-108; DXB-182;	SN-SOLUTION	C
	25898	MON 77790 HERBICIDE	GPI-132; DXB-82;	SN-SOLUTION	C
	25604	ROUNDUP FAST FORWARD PREHARVEST HERBICIDE	GPI-300; GLG-16;	SN-SOLUTION	C
	25795	ROUNDUP FASTFORWARD PRESEED	GPI-300; GLG-10;	SN-SOLUTION	C
	25918	MON 77759 WATER SOLUBLE HERBICIDE	GPI-300; GLG-36;	SN-SOLUTION	C
	26625	MON 78027 WATER SOLUBLE HERBICIDE	GPI-180; GLG-131;	SN-SOLUTION	C
	26920	ROUNDUP TRANSORB MAX LIQUID HERBICIDE	GPI-480;	SN-SOLUTION	C
	29841	MON 76431 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C
	29868	MON 76429 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C
	19899	VISION SILVICULTURE HERBICIDE	GPI-356;	SN-SOLUTION	C+R
	25344	ROUNDUP TRANSORB LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C+R
	27487	ROUNDUP WEATHERMAX WITH TRANSORB 2 TECHNOLOGY LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27736	VISIONMAX SILVICULTURE HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27764	ROUNDUP ULTRA LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	27946	RENEGADE HC LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28198	ROUNDUP TRANSORB HC LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28486	ROUNDUP ULTRA 2 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28487	RT/540 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28608	MON 79828 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	28609	MON 79791 LIQUID HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	29498	START UP HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	30104	MON 76669	GPP-540;	SN-SOLUTION	C+R
	32209	POWERMAX HERBICIDE	GPP-540;	SN-SOLUTION	C+R
	32356	ROUNDUP CUSTOM FOR AQUATIC AND TERRESTRIAL USE	GPI-;	SN-SOLUTION	R

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		LIQUID HERBICIDE			
NEWAGCO INC	29290	MPOWER GLYPHOSATE	GPI-356;	SN-SOLUTION	C
NUFARM AGRICULTURE INC.	30870	GLYKAMBA HERBICIDE	GPI-194; DIC-46;	SN-SOLUTION	C
	25866	NUFARM CREDIT LIQUID HERBICIDE	GPI-356;	SN-SOLUTION	C
	27950	CREDIT PLUS LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C
	29124	CREDIT 45 HERBICIDE	GPI-450;	SN-SOLUTION	C
	29125	NUFARM CREDIT 360 LIQUID HERBICIDE	GPI-360;	SN-SOLUTION	C
	29470	NUGLO HERBICIDE	GPI-450;	SN-SOLUTION	C
	29479	POLARIS	GPI-360;	SN-SOLUTION	C
	29480	NUFARM GLYPHOSATE 360 HERBICIDE	GPI-360;	SN-SOLUTION	C
	29888	CREDIT XTREME HERBICIDE	GPO-540;	SN-SOLUTION	C
	31316	CARNIVAL 540 HERBICIDE	GPO-540;	SN-SOLUTION	C
PRODUCTIERRA	31063	SMOKE 41% GLYPHOSATE	GPI-360;	SN-SOLUTION	C
RACK PETROLEUM LTD.	30442	THE RACK GLYPHOSATE	GPI-360;	SN-SOLUTION	C
	31314	RACKETEER	GPI-360;	SN-SOLUTION	C
SHARDA CROPCHEM LIMITED	31493	SHARDA GLYPHOSATE 360	GPI-360;	SN-SOLUTION	C
	32122	GLYFO SILVI HERBICIDE	GPI-360;	SN-SOLUTION	C+R
SYNGENTA CANADA INC.	29341	HALEX GT HERBICIDE	MER-25; GPP-250; AME-250;	SN-SOLUTION	C
	29552	TAKKLE HERBICIDE	GPI-140; DIC-70;	SN-SOLUTION	C
	30412	FLEXSTAR GT HERBICIDE	GPM-271; FOF-67;	SN-SOLUTION	C
	28802	CYCLE HERBICIDE	GPP-500;	SN-SOLUTION	C
	31711	CALLISTO GT HERBICIDE	MER-45.5; GPP-455;	SU-SUSPENSION	C
	27192	TOUCHDOWN IQ LIQUID HERBICIDE	GPM-360;	SN-SOLUTION	C+R
	28072	TOUCHDOWN TOTAL HERBICIDE	GPP-500;	SN-SOLUTION	C+R
	29201	TRAXION HERBICIDE	GPP-500;	SN-SOLUTION	C+R
TERAGRO INC	29022	WEED-MASTER GLYPHOSATE 41 HERBICIDE	GPS-356;	SN-SOLUTION	C
	29009	WEED-MASTER GLYPHOSATE FORESTRY HERBICIDE	GPI-356;	SN-SOLUTION	C+R
UNITED PHOSPHORUS INC.	30366	GLYPHO 41 HERBICIDE	GPI-356;	SN-SOLUTION	C+R
UNIVAR CANADA LTD.	32228	GUARDSMAN GLYPHOSATE	GPO-540;	SN-SOLUTION	C
DOW AGROSCIENCES CANADA INC.	27351	GLYPHOSATE 18% HERBICIDE SOLUTION CONCENTRATE	GPI-143;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	27352	GLYPHOSATE 0.96% HERBICIDE READY-TO-USE	GPI-7;	SN-SOLUTION	D
FMC CORPORATION	26609	GLYFOS HERBICIDE 143 CONCENTRATE	GPI-143;	SN-SOLUTION	D
	26610	GLYFOS HERBICIDE 7 READY-TO-USE	GPI-7;	SN-SOLUTION	D
	26827	GLYFOS CONCENTRATE 356 HERBICIDE	GPI-356;	SN-SOLUTION	D
MONSANTO CANADA INC.	22627	ROUNDUP CONCENTRATE NON-SELECTIVE HERBICIDE	GPI-143;	SN-SOLUTION	D
	22759	ROUNDUP SUPER CONCENTRATE GRASS & WEED CONTROL	GPI-356;	SN-SOLUTION	D
	22807	ROUNDUP READY TO USE NON-SELECTIVE HERBICIDE WITH FASTACT FOAM	GPI-7;	SN-SOLUTION	D
	24299	ROUNDUP READY-TO-USE GRASS & WEED CONTROL WITH FASTACT FOAM	GPI-7;	SN-SOLUTION	D
	26263	ROUNDUP READY-TO-USE WITH FASTACT FOAM PULL'N SPRAY NON-SELECTIVE HERBICIDE	GPI-7;	SN-SOLUTION	D
	27460	ROUNDUP READY-TO-USE NON-SELECTIVE HERBICIDE	GPI-7.2;	SN-SOLUTION	D
	27506	ROUNDUP READY-TO-USE PULL'N SPRAY NON-SELECTIVE HERBICIDE	GPI-14.0;	SN-SOLUTION	D
	27507	ROUNDUP READY-TO-USE PULL'N SPRAY TOUGH BRUSH & POISON IVY CONTROL NON-SELECTIVE HERBICIDE	GPI-14.0;	SN-SOLUTION	D
	28974	ROUNDUP PUMP 'N GO	GPI-7;	SN-SOLUTION	D
	29003	ROUNDUP READY-TO-USE POISON IVY & BRUSH CONTROL NON-SELECTIVE HERBICIDE	GPI-14;	SN-SOLUTION	D
	29034	ROUNDUP READY-TO-USE POISON IVY & BRUSH CONTROL WITH QUICK CONNECT SPRAYER	GPI-14;	SN-SOLUTION	D
	31153	REFILL FOR ROUNDUP READY-TO-USE WITH WAND APPLICATOR	GPI-7.0;	SN-SOLUTION	D
	31154	ROUNDUP READY-TO-USE WITH WAND APPLICATOR	GPI-7.0;	SN-SOLUTION	D
	31514	ROUNDUP READY-TO-USE REFILL	GPI-7;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	31997	ROUNDUP READY-TO-USE TOUGH BRUSH & POISON IVY CONTROL WITH WAND APPLICATOR	GPI-14.0;	SN-SOLUTION	D
	32041	REFILL FOR ROUNDUP READY-TO-USE TOUGH BRUSH & POISON IVY CONTROL WITH WAND APPLICATOR	GPI-14;	SN-SOLUTION	D
	23786	ROUNDUP QUIK STIK NON-SELECTIVE HERBICIDE TABLETS	GPS-60;	TA-TABLET	D
LES PRODUITS DE CONTROLE SUPERIEUR INC/SUPERIOR CONTROL PRODUCTS INC	28464	TOTALEX CONCENTRATE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-143;	SN-SOLUTION	D
	28467	BYEBYE WEED CONCENTRATE BRUSH, GRASS & WEED KILLER	GPI-143;	SN-SOLUTION	D
	28469	BYEBYE WEED READY-TO-USE BRUSH, GRASS & WEED KILLER	GPI-7;	SN-SOLUTION	D
	28470	TOTALEX READY-TO-USE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-7;	SN-SOLUTION	D
	28471	TOTALEX SUPER CONCENTRATE BRUSH, GRASS & WEED KILLER HOME GARDENER	GPI-356;	SN-SOLUTION	D
	28472	BYEBYE WEED SUPER CONCENTRATE BRUSH, GRASS & WEED KILLER	GPI-356;	SN-SOLUTION	D
	28574	TOTALEX RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER HOME	GPI-7.0;	SN-SOLUTION	D
	28575	BYEBYE WEED RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER	GPI-7.0;	SN-SOLUTION	D
	28576	TOTALEX EXTRA STRENGTH RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER SPRAYER HOME GARDENER	GPI-14;	SN-SOLUTION	D
	28577	TOTALEX EXTRA STRENGTH RTU BRUSH, GRASS & WEED KILLER WITH 1 TOUCH POWER	GPI-14;	SN-SOLUTION	D

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
		SPRAYER VIRTERRA			
SURE-GRO IP INC.	27013	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER READY TO USE	GPI-7;	SN-SOLUTION	D
	27014	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER CONCENTRATE	GPI-143;	SN-SOLUTION	D
	27015	LATER'S GRASS & WEED KILLER SUPER CONCENTRATE	GPI-356;	SN-SOLUTION	D
	29580	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER READY TO USE BATTERY POWERED	GPI-7;	SN-SOLUTION	D
	31023	SMARTONES WIPEOUT MAX	GPI-7.0;	SN-SOLUTION	D
	32090	WILSON TOTAL WIPEOUT MAX GRASS & WEED KILLER REFILL	GPI-7;	SN-SOLUTION	D
DOW AGROSCIENCES CANADA INC.	26449	GLYPHOSATE 62% SOLUTION MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
	27074	VANTAGE HERBICIDE SOLUTION MANUFACTURING CONCENTRATE	GPI-356;	SN-SOLUTION	M
	27075	VANTAGE PLUS HERBICIDE SOLUTION MANUFACTURING CONCENTRATE	GPI-360;	SN-SOLUTION	M
	28963	GLYPHOSATE 85% MANUFACTURING CONCENTRATE	GPS-85;	SN-SOLUTION	M
	28783	GF-1667 HERBICIDE MANUFACTURING CONCENTRATE	GPX-49;	SN-SOLUTION	M
FMC CORPORATION	25600	GLYPHOSATE CONCENTRATE HERBICIDE	GPI-46.3;	SN-SOLUTION	M
	27497	GLYFOS 356 MUC	GPI-356;	SN-SOLUTION	M
MONSANTO CANADA INC.	21061	MON 0139 SOLUTION HERBICIDE MANUFACTURING CONCENTRATE	GPI-46.0;	SN-SOLUTION	M
	26919	MON 77945 HERBICIDE MANUFACTURING CONCENTRATE SOLUTION	GPI-46;	SN-SOLUTION	M
	28625	MON 78087 HERBICIDE MANUFACTURING CONCENTRATE	GPI-356;	SN-SOLUTION	M
	32273	GLY 135EA HERBICIDE MANUFACTURING CONCENTRATE	GPI-45.6;	SN-SOLUTION	M

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
	27485	MON 78623 HERBICIDE MANUFACTURING CONCENTRATE	GPP-47.3;	SN-SOLUTION	M
	28603	MON 79380 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	28604	MON 79582 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	28605	MON 79544 HERBICIDE MANUFACTURING CONCENTRATE	GPP-540;	SN-SOLUTION	M
	27183	MON 77973 HERBICIDE MANUFACTURING CONCENTRATE	GPS-85;	SN-SOLUTION	M
NUA	29123	NUFARM GLYPHOSATE IPA MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
SYNGENTA CANADA INC.	27871	GLYPHOSATE 600 SL MANUFACTURING CONCENTRATE	GPS-600;	SN-SOLUTION	M
WMW	29719	TERAGRO GLYPHOSATE MANUFACTURING CONCENTRATE	GPI-46;	SN-SOLUTION	M
ALBAUGH LLC	28321	CLEAROUT GLYPHOSATE TECHNICAL	GPS-94.8;	SO-SOLID	T
AGROMARKETING CO. INC.	29645	NASA GLYPHOSATE TECHNICAL	GPS-96.37;	SO-SOLID	T
CONSUS CHEMICALS, LLC.	31728	CONSUS GLYPHOSATE TECHNICAL	GPS-96.7;	SO-SOLID	T
DOW AGROSCIENCES CANADA INC.	26450	GLYPHOSATE TECHNICAL HERBICIDE	GPS-96.3;	SO-SOLID	T
	28967	TECHNICAL GLYPHOSATE HERBICIDE	GPS-96.2;	SO-SOLID	T
FMC CORPORATION	24337	GLYPHOSATE TECHNICAL	GPS-85.8;	SO-SOLID	T
	29143	GLYFOS SOLUBLE CONCENTRATE HERBICIDE 2	GPS-97.9;	SO-SOLID	T
	29326	CHEMINOVA GLYPHOSATE TECHNICAL II	GPS-95.7;	SO-SOLID	T
	29530	CHEMINOVA GLYPHOSATE TECHNICAL III	GPS-98.2;	SO-SOLID	T
JOINT GLYPHOSATE TASK FORCE, LLC	30638	JOINT GLYPHOSATE TECHNICAL	GPS-96.3;	SO-SOLID	T
LIBERTAS NOW INC.	29265	KNOCKOUT TECH	GPS-98.1;	SO-SOLID	T
MEY CORPORATION	29799	MEY CORP GLYPHOSATE TECHNICAL	GPS-98.5;	SO-SOLID	T
	30099	MGT GLYPHOSATE TECHNICAL	GPS-96.4;	SO-SOLID	T
	30617	MEY GLYPHOSATE SHANRG TECHNICAL	GPS-97.59;	SO-SOLID	T

Registrant Name	Registration Number	Product Name	Guarantee[1] (g a.e./L)	Formulation	Marketing Class[2]
MONSANTO CANADA INC.	19535	GLYPHOSATE TECHNICAL GRADE	GPS-96.3;	SO-SOLID	T
NEWAGCO INC	29381	NEWAGCO GLYPHOSATE TECHNICAL	GPS-96.0;	SO-SOLID	T
NUFARM AGRICULTURE INC.	28857	NUFARM GLYPHOSATE TECHNICAL ACID	GPS-96.5;	SO-SOLID	T
PRODUCTIERRA	31062	PRODUCTIERRA GLYPHOSATE TECHNICAL	GPS-98.0;	SO-SOLID	T
SHARDA CROPCHEM LIMITED	29980	SHARDA GLYPHOSATE TECHNICAL HERBICIDE	GPS-96.2;	SO-SOLID	T
SYNGENTA CANADA INC.	28983	TECHNICAL TOUCHDOWN HERBICIDE	GPS-97.1;	SO-SOLID	T
	29540	TOUCHDOWN TECHNICAL HERBICIDE	GPS-99;	SO-SOLID	T
UPI GLYPHOSATE TECHNICAL HERBICIDE	30634	UPI GLYPHOSATE TECHNICAL HERBICIDE	GPS-97.7;	SO-SOLID	T
TERAGRO INC	28882	GLYPHOSATE TECHNICAL HERBICIDE	GPS-97.5;	SO-SOLID	T

[1] GPS = glyphosate acid, GPI = glyphosate isopropylamine or ethnolamine salt, GPM = glyphosate mono-ammonium or diammonium salt, GPP = glyphosate potassium salt, GPX = glyphosate dimethylsulfonium salt, and GPO = GPI + GPP. Note that GPT (glyphosate trimethylsulfonium salt) has been voluntarily discontinued by the registrant Syngenta Canada Inc.

[2] C = Commercial Class, C+R = Commercial and Restricted Class, D = Domestic Class, M = Manufacturing Concentrate, T = Technical grade active ingredient.

[3] AME = s-metolachlor, DIC = dicamba, DIQ = diquat, DXB = 2,4-D (isomer specific), FOF = fomesafen, GLG = glufosinate ammonium and MER = mesotrione.

Appendix III Summary of Species sensitivity Distribution Toxicity Data

Table 1 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [1] or the most sensitive endpoints are listed by taxonomic group for Fish, Aquatic Invertebrates and Amphibians [*]

Test material	Exposure	Freshwater invertebrates (mg a.e./L)[B]	Freshwater fish (mg a.e./L)[C]	Marine fish (mg a.e./L)[C]	Marine invertebrates (mg a.e./L)[B]	Amphibians (mg a.e./L)[C]	Amphibians Mesocosm/field (mg a.e./L)[C]
TGAI	Acute	HC_5: 15.9	HC_5: 70	HC_5: 19.9	HC_5: 4.7	HC_5: 14.9	-
	Chronic	NOEC: 13.0	NOEC: 22.4	NOEC: 0.1	-	-	-
EUP NON POEA	Acute	HC_5: 24.4	HC_5: 2.3	LC_{50}: 114.6	EC_{50}: 23.2	HC_5: 13.9	-
	Chronic	EC_{50}: 44.0	-	-	-	-	-
EUP WITH POEA	Acute	HC_5: 0.1	HC_5: 2.2	HC_5: 3.0	HC_5: 0.1	HC_5: 0.73	HC_5: 3.7 HC_5: 3.3 (kg a.e/ha)
	Chronic	NOEC: 0.2	NOEC: 0.28	-	-	HC_5: 0.43	HC_5: 1.9
AMPA	Acute	LC_{50}: 316.0	LC_{50}: 274.0	-	EC_{50}: 97.0	-	-
	Chronic	-	-	-	-		-
POEA	Acute	HC_5: 0.004	HC_5: 0.2	HC_5: 2.0	EC_{50}: 0.6	HC_5: 0.3	-
	Chronic	-	-	-	-	-	-

[*]Where SSDs could not be determined, the most sensitive species endpoint value is reported; [1]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values.
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Table 2 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [1] or the most sensitive endpoints are listed by taxonomic group for Aquatic Plants, Algae, Terrestrial Plants [*]

Test material	Exposure	Freshwater Algae (mg a.e./L)[B]	Freshwater Plants (mg a.e./L)	Marine Algae (mg a.e./L)	Snails (mg a.e./L)
TGAI	Acute	HC_5: 6.6 EC_{50}: 10.1	EC_{50}: 17.3 Er_{50}: 0.38 kg a.e./ha	EC_{50}: 3.35	-
	Chronic	HC_5:21.6	-	EC_{50}:101.5	NOEC: 1000
EUP NON POEA	Acute	EC_{50}: 37	-	-	-
	Chronic	-	-	-	NOEC: 29.7 NOEC: 219 (mg a.e./kg soil)
EUP WITH POEA	Acute	HC_5: 0.1	EC_{50}: 2.1	EC_{50}: 0.43	LC_{50}: 2.3
	Chronic	HC_5:0.3		EC_{50}: 8.3	NOEC: 8.55
EUP NON POEA and WITH POEA	Acute	-	-	-	-

Test material	Exposure	Freshwater Algae (mg a.e./L)[B]	Freshwater Plants (mg a.e./L)	Marine Algae (mg a.e./L)	Snails (mg a.e./L)
AMPA	Acute	EC_{50}: 73	-	-	-
	Chronic	-	-	-	-
POEA	Acute	EC_{50}: 4	-	EC_{50}: 3.4	-

[*]Where SSDs could not be determined, the most sensitive species endpoint value is reported; [1]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values;
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Table 3 Revised summary of Species Sensitivity Distribution (SSDs) toxicity data analysis for glyphosate herbicide: HC_5 [1] or the most sensitive endpoints are listed by taxonomic group for Terrestrial Plants and Terrestrial Invertebrates.

Test material	Exposure	Terrestrial Plants (SE) EC_{50} (kg a.e/ha)	Terrestrial plants EC_{25} Mixed[D] (kg a.c/ha)	Terrestrial plants E_{C50} Mixed[D] (kg a.c/ha)	Earthworms (mg a.e./kg soil)
TGAI	Acute	EC_{50}: 0.07	-		690
	Chronic	-	-		-
EUP NON POEA	Acute	EC_{50}: 4.48	-		-
	Chronic	-	-		-
EUP WITH POEA	Acute	-	HD_5 = 0.035		0.253
	Chronic	-	-		-
EUP NON POEA and WITH POEA	Acute	-	HD_5 = 0.037	HD_5 = 0.0658	-

(SE) = seedling emergence, (VV) = vegetative vigor; [*]Where SSDs could not be determined, the most sensitive species endpoint value is reported; [1]Hazardous concentration to 5% of species; POEA is a formulant, POEA concentrations cannot be directly compared to other data as the concentration in a formulation varies and not specified; [B] HC_5 is derived from EC_{50} values; [C] HC_5 is derived from LC_{50} values; [D]Mixed = Crop and non-crop plants combined. Yellow highlight: most sensitive acute and chronic endpoint.
TGAI = Technical grade active ingredient, EUP NON POEA = End-use product that does not contain polyethoxylated tallow amine compound in their formulation, EUP WITH POEA = End-use product that does contain polyethoxylated tallow amine compound in their formulation, AMPA = aminmethylphosphonic acid compound, POEA = polyethoxylated tallow amine

Appendix IV Label Amendments for Products Containing Glyphosate

The label amendments presented below do not include all label requirements for individual products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements.

A) Label Amendments for Glyphosate Technical Products

The following label amendments are required on the Glyphosate Technical labels:

1) Add to the primary panel of the Technical product labels:

   The signal words "DANGER – EYE IRRITANT", and accompanying glyphs.

2) Before **STORAGE section, Add** the title "**ENVIRONMENTAL HAZARDS**" and the following statement:

   - **TOXIC** to non-target terrestrial plants
   - **TOXIC** to aquatic organisms

3) **Remove** the following statement under the "**DISPOSAL AND DECONTAMINATION**"

   "Canadian formulators of this technical should dispose of unwanted active and containers in accordance with municipal or provincial regulations. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in the case of a spill, and for clean-up of spills."

   and replace it with the following statement:

   "Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean up of spills, contact the manufacturer or the provincial regulatory agency."

B) For Domestic Products Containing Glyphosate

For all end-use products, the following statement is required:

"Glyphosate is not to be applied using hand-wicking or hand-daubing methods."

C) For Commercial and Agricultural Class Products Containing Glyphosate

1) Add to DIRECTIONS FOR USE:

For all end-use products, the following statement is required:

"Glyphosate is not to be applied using hand-wicking or hand-daubing methods."

Restricted Entry Intervals

"The restricted entry interval is 12 hours after application for all agricultural uses."

2) **Add to Use Precautions**

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

3) Add the following to ENVIRONMENTAL HAZARDS:

- **TOXIC** to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.
- To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay.
- Avoid application when heavy rain is forecast.
- Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

4) **Add to DIRECTIONS FOR USE**

The following statement is required for all agricultural and commercial pesticide products:

- **As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests**
- **DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.**

5) Add to **DIRECTIONS FOR USE**

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. Boom height must be 60 cm or less above the crop or ground.

Airblast or mist blower application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side. For airblast applications, turn off outward pointing nozzles at row ends and outer rows.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment, inter-row hooded sprayer, low-clearance hooded or shielded sprayers that ensure spray drift does not come in contact with orchard crop fruit or foliage, soil drench and soil incorporation.

For application to rights-of-way and for forestry uses, buffer zones for protection of sensitive terrestrial habitats are not required; however, the best available application strategies which minimize off-site drift, including meteorological conditions (for example, wind direction, low wind speed) and spray equipment (for example, coarse droplet sizes, minimizing height above canopy), should be used. Applicators must, however, observe the specified buffer zones for protection of sensitive aquatic habitats.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, wetlands and estuarine/marine water bodies).

Table 1 Buffer Zones for the Protection of Aquatic and Terrestrial Habitats from Spray Drift of Glyphosate Products Formulated with POEA

Agricultural, forestry and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Agricultural crop system and ground boom application method				
Rye, cranberry, pasture, summer fallow, all other crops for pre-seeding treatments only, filberts or hazelnut at pre-seeding only, ginseng new garden		1	1	1
Ginseng - existing established garden, Canola – Roundup Ready hybrid for seed production		2	1	1
Filberts or hazelnut, sugar beets (glyphosate tolerant varieties)		4	1	1
Corn (glyphosate non-tolerant varieties including grain, silage and ornamental types), sugar beet (glyphosate non-tolerant varieties), strawberry, blueberry highbush and lowbush, walnut, chestnut, Japanese heartnut, Turf grass (prior to establishment or renovation)		2	1	2
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils, chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet, sorghum (grain) (not for use as a forage crop), asparagus, corn (glyphosate tolerant varieties), forage grasses and legume including seed production		3	1	2
Canola (glyphosate tolerant varieties), soybean (glyphosate tolerant varieties)		4	1	2
Apple, apricot, cherry (sweet/sour), peaches, pears, plums, grapes		3	1	3
Agricultural crop system and airblast application method (including mist blower)				
Pasture		1	20	30
Turfgrass (Prior to establishment or renovation)		2	25	35
Forest plant system and ground boom application method				
Forest and woodlands > 500 ha Site preparation		2	1	NR
Forest plant system and airblast application method (including mist blower)				
Forest and woodlands > 500 ha Site preparation		2	1	NR
Non-cropland system and ground boom application method				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	3*
Non-cropland system and airblast application method (including mist blower)				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	30*
Agricultural crop system and aerial application method	**Wing type**			
Rye, corn (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet , sorghum (grain) (not for use as a forage crop), sugar beet (glyphosate non-tolerant varieties), all other crops for pre-seeding treatments only	Fixed and rotary wing	1	15	20

Agricultural, forestry and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Canola (glyphosate tolerant varieties)	Fixed and rotary wing	3	20	40
Sugar beets (glyphosate tolerant varieties)	Fixed wing	2	20	30
	Rotary wing	2	15	30
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils	Fixed wing	2	20	35
	Rotary wing	2	20	30
Forage grasses and legume including seed production	Fixed and rotary wing	1	20	40
Soybean (glyphosate tolerant varieties)	Fixed wing	3	20	45
	Rotary wing	3	20	40
Summer fallow	Fixed wing	1	20	45
	Rotary wing	1	20	40
Corn (glyphosate tolerant varieties)	Fixed wing	2	20	50
	Rotary wing	2	20	45
Pasture	Fixed wing	1	30	70
	Rotary wing	1	30	55
Forestry system and aerial application method				
Forest and woodlands >500 ha Site preparation	Fixed wing	2	10	NR
	Rotary wing	2	1	NR
Forest and woodlands <500 ha Site preparation	Fixed wing	2	5	NR
	Rotary wing	2	1	NR
Non-cropland system and aerial application method				
Non-crop land and industrial uses: rights-of way areas only	Fixed wing	3	100	NR
	Rotary wing	3	60	NR

* Buffer zones for the protection of terrestrial habitats are not required for forestry uses or for use on rights-of-way including railroad ballast, rail and hydro rights-of-way, utility easements, roads, and training grounds and firing ranges on military bases.
NR = Buffer zones for the protection of terrestrial habitats are not required for forestry uses.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

Table 2 Buffer Zones for the Protection of Aquatic and Terrestrial Habitats from Spray Drift of Glyphosate Products without POEA

Agricultural and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Agricultural crop system and ground boom application method				
Rye, cranberry, pasture, summer fallow, pasture, all other crops for pre-seeding treatments only, filberts or hazelnut pre-seeding only, ginseng new garden		1	1	1
Ginseng - existing established garden, Canola – Roundup Ready hybrid for seed production		2	1	1
Filberts or hazelnut, sugar beets (glyphosate tolerant varieties)		4	1	1
Corn (glyphosate non-tolerant varieties including grain, silage and ornamental types), sugar beet (glyphosate non-tolerant varieties), strawberry, blueberry highbush and lowbush, walnut, chestnut, Japanese heartnut, Turf grass (prior to establishment or renovation)		2	1	2
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils, chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet, sorghum (grain) (not for use as a forage crop), asparagus, corn (glyphosate tolerant varieties), forage grasses and legume including seed production		3	1	2
Canola (glyphosate tolerant varieties), soybean (glyphosate tolerant varieties)		4	1	2
Apple, apricot, cherry (sweet/sour), peaches, pears, plums, grapes		3	1	3
Agricultural crop system and airblast application method (including mist blower)				
Pasture		1	20	30
Turfgrass (Prior to establishment or renovation)		2	25	35
Non-cropland system and ground boom application method				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	1	3
Non-cropland system and airblast application method (including mist blower)				
Non-crop land and industrial uses: Industrial and rights of way areas, Recreational and public areas		3	20	30
Agricultural crop system and aerial application method				
Rye, corn (glyphosate non-tolerant varieties), corn-sweet (glyphosate tolerant varieties), chickpea, lupin (dried), fava bean (dried), mustard (yellow/white, brown, oriental), pearl millet , sorghum (grain) (not for use as a forage crop), sugar beet (glyphosate non-tolerant varieties), all other crops for pre-seeding treatments only	Fixed and rotary wing	1	15	20

Agricultural and non-cropland systems		Maximum number of applications	Buffer Zones (metres) Required for the Protection of:	
			Aquatic habitats	Terrestrial habitats
Sugar beets (glyphosate tolerant varieties)	Fixed wing	2	20	30
	Rotary wing	2	15	30
Wheat, barley, oats, soybean (glyphosate non-tolerant varieties), canola (glyphosate non-tolerant varieties), peas, dry beans, flax (including low linoleic acid varieties), lentils	Fixed wing	2	20	35
	Rotary wing	2	20	30
Forage grasses and legume including seed production	Fixed and rotary wing	1	20	40
Canola (glyphosate tolerant varieties)	Fixed and rotary wing	3	20	40
Soybean (glyphosate tolerant varieties)	Fixed wing	3	20	45
	Rotary wing	3	20	40
Summer fallow	Fixed wing	1	20	45
	Rotary wing	1	20	40
Corn (glyphosate tolerant varieties)	Fixed wing	2	20	50
	Rotary wing	2	20	45
Pasture	Fixed wing	1	30	70
	Rotary wing	1	30	55
Non-cropland system and aerial application method				
Non-crop land and industrial uses: rights-of way areas only	Fixed wing	3	100	NR
	Rotary wing	3	60	NR

* Buffer zones for the protection of terrestrial habitats are not required for use on rights-of-way including railroad ballast, rail and hydro rights-of-way, utility easements, roads, and training grounds and firing ranges on military bases.
NR = Buffer zones for the protection of terrestrial habitats are not required for forestry uses.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

References

Studies and Information Considered in Relation to Human Health Risk Assessment

Toxicology

A. List of Additional Studies/Information submitted by Registrant – Unpublished

PMRA Document Number	Reference
1644044	2007, Surfactant 8184-92, acute dermal toxicity study in rabbits, DACO: 4.6.2
1644045	2007, Surfactant 8184-92, acute dermal toxicity study in rats, DACO: 4.6.2
1817835	2007, Surfactant, 8184-92, acute inhalation toxicity study in rats, DACO: 4.6.3
1817836	2007, Surfactant, 8184-92, skin sensitization study in guinea pigs, DACO: 4.6.6
1817838	2007, Surfactant, 8184-92, acute eye irritation study in rabbits, DACO: 4.6.4
1817839	2008, Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats for experimental surfactant 8184-92, DACO: 4.7.7
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