GLYPHOSATE
HUMAN HEALTH BRIEFING

November 5th, 2015

Preliminary Human Health Risk Assessment

HED Risk assessment (includes all uses and current policies)

- Chronic Dietary: 23% cPAD (1-2 yr olds) and 9% (US POP); unrefined
- Aggregate (LOC = 100): 260 (1-2 yr olds) and 1300 (adults)

AMPA (glyphosate metabolite)

- Not included in US tolerances or Codex MRLs
  - AMPA: Low acute toxicity; subchronic- effects only at limit dose in rats and no effects in dogs; developmental toxicity in rats at limit dose and non-mutagenic.
  - Glyphosate PODs are protective as AMPA is less toxic
- Included in PMRA MRLs and risk assessment

Spray Drift assessment

- Registered turf use protective of potential spray drift exposures

Volatilization assessment

- Glyphosate was not included in volatilization screen as no hazard seen in route specific inhalation study (aerosol). In addition, glyphosate is not expected to significantly volatilize.

Preliminary Human Health Risk Assessment

Human milk analysis

- BEAD analyzed human milk samples collected by the National Childrens' Study for residues of glyphosate and glyphosate metabolites *N*-acetyl-glyphosate and AMPA
  - Total of 39 samples (from 39 mothers in the Miami area) were analyzed using a fully validated LC-MS/MS, which has a high level of specificity for the target analytes
  - No residues of glyphosate and its metabolites were detected at or above the LOD (glyphosate LOD = 3.3 ppb; *N*-acetyl-glyphosate and AMPA LOD = 10 ppb).
  - Frozen storage stability study is being conducted with control milk samples fortified with glyphosate, *N*-acetyl-glyphosate, and AMPA.
    - ✓ Fortified samples were analyzed after 4 months of storage and showed stability
    - ✓ Additional fortified samples will be analyzed after 8 months (October 2015) and 12 months (February 2016) of storage

Preliminary Human Health Risk Assessment

Human milk analysis

- McGuire *et al. (*Washington State University) collected milk and urine from 41 lactating mothers from 3 highly productive Ag areas in Washington State (known to routinely use glyphosate). According to McGuire:
  - Ten mothers live on or adjacent to a farm/ranch, 23 have conventional diets, and 5 had personally applied/mixed glyphosate in past
  - Analyses conducted via High Resolution LC-MS in Monsanto's St. Louis laboratory and independently verified by another laboratory
  - No residue of glyphosate and its metabolites were detected at or above the method LOD (glyphosate LOD = 2 ppb; *N*-acetyl-glyphosate and AMPA LOD = 10 ppb), even when found in corresponding mother's urine sample
  - None to low levels of glyphosate and its metabolites (up to 2 ppb) were detected in urine samples (glyphosate LOD = 0.02 ppb; *N*-acetyl-glyphosate and AMPA LOD = 0.03 ppb)
  - All analyses were performed within 2 months of sample collection

Preliminary Human Health Risk Assessment

Open Literature Study Review

- 67 studies reviewed in conjunction with PMRA (primary reviewer) from 62 individual references
  - Overall, most studies were deemed “unacceptable” for use in risk assessment based on the agency literature study guidance
  - No studies quantitatively impact the hazard characterization or human health risk assessment
- Since review with PMRA (2012), an additional 399 studies have been reviewed
  - Search of PubMed from Jan 2012 to Oct 2015 = 392 journal articles
  - Cross-referenced list with studies submitted by various NGOs and added another 7 studies
  - Utilized systematic review process to determine whether articles were relevant to human health risk assessment
  - No studies quantitatively impact the hazard characterization or human health risk assessment

Preliminary Human Health Risk Assessment

Tier II Incident and Epidemiology Report

- Tier II incident analysis found that the acute health effects reported in the queried incident databases were generally mild/minor to moderate and resolved rapidly.
- 55 epidemiology studies examining potential cancer and non-cancer, chronic health effects
  - Overall HED could not conclude glyphosate plays a role in any of the health outcomes studied across the available epidemiologic data
  - PMRA relying on HED report
- Only one study reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes
- Case control studies did show non-statistically significant increase in non-Hodgkins lymphoma associated with glyphosate exposure
- Glyphosate was included in the Agricultural Health Study

EDSP Tier 1 Screen

- No evidence of potential interaction with the estrogen, androgen or thyroid pathways
- Tier 2 testing is not recommended for glyphosate.

Cancer Assessment: History

1985 Classification – Group C Carcinogen; Possible Human Carcinogen

- Male mouse kidney tumors (1/49 control; 0/49; 1/50 and 3/50)
- No evidence of carcinogenicity in female mice or male/female rats

PWG – Evaluation of additional kidney slides of all treated groups

- Tumors Not Treatment- Related- No trend or pairwise statistical significance; no preneoplastic lesions; lack of multiple tumors

1986 – SAP Evaluation

Group D Chemical; Not Classifiable to Human carcinogenicity

- Renal tumors equivocal; no statistical significance. DCI for repeat studies

1991 CPRC Review

Group C: Chemical; Possible Human Carcinogen

- Equivocal (kidney) tumor response in male mice
- Lack of statistical significance – pairwise
- No pre-neoplastic lesions
- No evidence of carcinogenicity in female mice, male or female rats
- No mutagenicity/genotoxicity concerns
- No SAR concerns

IARC Evaluation - 2015

Group 2A- Probable Human Carcinogen (Group 2A)

Limited Evidence in Humans

- Positive association for Non-Hodgkin Lymphoma
- Case-control – Canada
- Case-control- Sweden
- Case-control – U.S.A
- Meta-analysis

Sufficient Evidence in Animals

- Positive trend for renal carcinoma and combined adenoma/carcinoma in male mice in one study
- Positive trend for hemangiosarcomas in male mice in the second study

Strong evidence for genotoxicity

- Glyphosate and glyphosate-formulations
- DNA and chromosomal damage in mammals *in vivo* and in humans and animals *in vitro*.

New Data Evaluated in 2015

1991 CPRC Data Set

- 1 Mouse and 2 Rat carcinogenicity studies submitted to OPP
- Mutagenicity studies submitted to OPP

IARC Data Set

- 28 Epidemiology studies
- 2 Mouse carcinogenicity studies (1 study submitted to JMPR but not to OPP)
- 4 Rat carcinogenicity studies (2 studies submitted to JMPR but not to OPP)
- Mutagenicity studies in the published literature

2015 CARC Data Set

- 31 Epidemiology studies
- 4 Mouse cancer studies
- 7 Rat cancer studies
- 54 Mutagenicity studies

Note: 5 animal studies cited in Greim *et al* 2015 and numerous genotoxicity studies by Kirke *et al* 2013 review articles were not evaluated by IARC

CARC Evaluation

Evidence in Humans

- No association between glyphosate exposure and cancer of: the oral cavity; esophagus, stomach; colon; rectum; colorectum; lung; pancreas; kidney; bladder; prostate; breast; cutaneous melanoma; or soft tissue sarcoma
- No association between glyphosate exposure and brain cancer (gliomas); leukemia or multiple myeloma
- NHL:
  - No significant association between glyhphosate exposure and NHL in 4 case-control studies
  - No association with 2 case-control studies and in the AHS prospective cohort study
  - A suggestive association in 2 case-control studies in Sweden, 1 in Canada, and 1 USA study
- Inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL
  - CARC does agree with IARC in that epidemiological evidence is limited, thus cannot support a direct causal association at this point in time
- The literature will continue to be monitored for studies related to glyphosate and risk of NHL

CARC Evaluation (continued)

Evidence in Animals

- No evidence of carcinogenicity in 4 studies with CD-1 mice following dietary administration at doses ranging from 85.0 to 4945 mg/kg/day for up to 2 years.
- No evidence of carcinogenicity in 7 studies in Sprague Dawley or Wistar rats following dietary administration at doses ranging from 3.0 to 1500 mg/kg/day for up to 2 years.

Evidence for Mutagenicity

- No mutagenic or genotoxic concern in a wide range of *in vivo* and in vitro assays: negative for gene mutation, chromosomal damage, DNA damage and repair

2005 Cancer Guidelines: “Not Likely to be Carcinogenic to Humans”

Epidemiology Studies: IARC and CARC

1. **Case-control - Canada**: exposed: 51 cases/133 controls (McDuffie *et al.* 2001)

IARC: Positive association only for those with more than 2/days/year exposure: ≤2days/year OR=1.00 (0.63 – 1.57) >2 days/year OR= 2.12 (1.20-3.73).

CARC: Increase not statistically significant; Univariate: OR= 1.26; 95% CI=0.87-1.8 Multivariate: OR=1.20; 95% CI=0.87-1.8).

Note: IARC only included the >2 days/year and no adjustments for other pesticides

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2. **Case-Control – Sweden**: exposed: 8 cases/8 controls (Hardell *et al.* 2002)

IARC: Excess risk based on pooled analysis of 2 studies [NHL and HCL (a NHL variant)].

CARC: The excess risk (OR= 3.04; 95% CI=1.08 – 8.52) in a univariate analysis attenuated when study site, vital status, and exposure to other pesticides were taken into a multivariate analysis (OR=1.85; 95% CI=0.55-6.20)

Epidemiology Studies: IARC and CARC

3. **Case-control – U.S.A**: exposed: 36 cases/61 controls (De Roos *et al.* 2003)

IARC: Increase in logistic regression analysis (OR=2.1; 95% CI= 1.1- 4.0)

CARC: Non significant in the hierarchical regression (OR=1.6; 95% CI=0.9–2.8)

Note: IARC used the logistic analysis in their rationale, but not the hierarchical analysis which is used to adjust for exposure to other pesticides

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4. **Case-control – Sweden**: exposed: 29 cases/18 controls (Eriksson *et al.* 2008)

IARC: Increase in univariate (OR=2.02; 95% CI=1.10-3.71) and multivariate analysis (OR=1.51; 95% CI=0.77-2.94)

CARC: Suggestive; statistical significance only in univariate but not in multivariate

Note: IARC noted the non-significance but included in their rationale.

Assessments: IARC and CARC

IARC: assessment looks at the intrinsic **'hazard'** of a chemical as a cancer-causing agent only according to its "preamble". Other components of toxicity/carcinogenicity are not taken into account. Reviews only reports/studies published in the open literature.

Preamble: "*sufficient evidence of carcinogenicity*" if tumors occur in:

- 1) two or more species of animals;
- 2) **two or more independent studies in one species;** and/or
- 3) an increased incidence of tumors in both sexes of a single species

EPA: Weight-of-Evidence Approach

- Tumors in multiple species, strains, or both sexes;
- Dose-response;
- Progression of lesions from pre-neoplastic to benign to malignant;
- Proportion of malignant tumors;
- Reduced latency of neoplastic lesions;
- Both biological and statistical significance of the findings;
- Use of the background incidence (historical control) data;

Animal Studies: IARC and CARC

Male Mouse Kidney Tumor (1983 study)

IARC: Positive trend only for carcinoma and adenoma/carcinoma

CARC: Not treatment-related based on:

- No positive trend or pair-wise significance;
- No pre-neoplastic lesions;
- Low magnitude of response (6%) – 4x the Limit Dose;
- Incidences within historical control range; and
- Kidney tumors were not replicated in the same strain in the other 3 studies

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Male Mouse Hemangiosarcomas (1993 study)

IARC: Positive trend only for hemangiosarcomas

CARC: Not treatment-related based on:

- Tumors seen only at the limit dose;
- No pair-wise significance;
- Incidence (9%) was near or the same as the upper limit (0–8%);
- Tumors not seen in male mice in the same strain in the other 3 studies;
- Considerable inter-group variability in incidences in female mice;
- Both spontaneous/treatment-related tumors arising from endothelial cells;
- Appear in both sexes but are generally more common in males; and
- As vascular tumors, they can occur at different sites

Mutagenicity: IARC and CARC

IARC: There is strong evidence that exposure to glyphosate or glyphosate based formulations isgenotoxic.

- Studies that tested glyphosate-formulated products;
- Studies where the test material was not well-characterized;
- Focused on DNA damage as an endpoint (*e.g.*, comet assay);
- Studies with limitations confounding interpretation or results;
- Many negative studies (Kier and Kirkland (2013) not included in review

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CARC: No concern for mutagenicity or genotoxicity *in vivo* and *in vitro.* Negative for gene mutation, chromosomal damage, DNA damage and repair.

- Although some studies in the open literature reported positive findings these findings were not replicated in a number of assays.
- There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage

Summary

Epidemiological Studies

- No association between glyphosate exposure and site-specific cancer
- Case-control studies on NHL: Does not support a direct causal association
  - CARC does agree with IARC in that epidemiological evidence is limited, thus cannot support a direct causal association at this point in time
- Prospective cohort (AHS) study on NHL: No significant increased risk

Experimental Animals

- No evidence of carcinogenicity in male or female mice in 4 studies
- No evidence of carcinogenicity in male or female in 2 strain of rats in 7 studies

Mutagenicity

- No concern for mutagenicity/genotoxicity
- *Classification: Not Likely to be Carcinogenic to Humans*

Around the World with Glyphosate

- **Australia (2013):** Currently, the weight and strength of evidence does not support the conclusion that glyphosate causes cancer in either laboratory animals or humans (APVMA, 07/2013).
- **Canada (2015):** No evidence of carcinogenicity in mice and rats (PRVD 2015-01)
- **EU Regulation (CLP):** No classification
- **EFSA (2014):** Glyphosate does not show carcinogenic or mutagenic properties.
- **Germany (2014)**: Available data do not show carcinogenic or mutagenic properties of glyphosate.
- **JMPR/WHO (2004):** No evidence of carcinogenicity in rats or mice or mutagenicity
- **South Africa**: Glyphosate poses a minimal risk to users and the general public, provided it is used according to label instructions and safety statements.
- **U.S.A** : Cal/EPA intends to list the herbicide glyphosate – the active ingredient in RoundUp – as a carcinogenic chemical under the Proposition 65

Questions?