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)

Note: Few exposed cases; individual studies non-significant; large CI.

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 no 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-XX)
* **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 6