IARC	EFSA	EPA/OPP Draft	Comments
Human data. In summary, case–control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The AHS cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures. **Evaluation:** Sufficient evidence **Limited evidence ←** Inadequate evidence Evidence suggesting lack of carcinog'icity	**Human data.** Mink et al. (2012, ASB2014-9617) submitted a comprehensive review of epidemiologic studies of glyphosate and cancer. To examine potential cancer risks in humans they reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. They also reviewed relevant methodological and biomonitoring studies of glyphosate. The review found [no] consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or in children) or any site-specific cancer and exposure to glyphosate. [German report, p 70]	**Human data.** In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.	**Human data.** EPA/OPP presents mostly results for ever/never exposure and does not consistently pull out data from the studies that would provide a more in-depth picture of exposure-response. EPA/OPP discusses co-exposure to other pesticides as a general limitation but does not discuss the adjustments that some studies made for co-exposures. The draft also expresses concern for confounding but does not identify which pesticides are associated with NHL or other cancers. EPA/OPP and EFSA discuss "causal relationship" and "does not support a causal relationship" but do not seem to recognize the possibility of intermediate conclusions.
Animal data. There was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carcinoma is a rare tumour in this strain of mice. No significant increase in tumour incidence was seen in female mice in this study. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. No significant increase in tumour incidence was seen in female mice in this study. For the five feeding studies in rats, two studies in the Sprague-Dawley strain	**Animal data.** Taking all this information together, a treatment-related effect in the study by (2001, ASB2012-11491) in Swiss albino mice cannot be completely excluded. However, the weak increase in malignant lymphoma even over the historical control of the performing laboratory was clearly confined to this single study and strain since it was not reproducible in four other valid long-term studies. Thus, there is only very limited evidence of a carcinogenic potential of glyphosate as a high-dose phenomenon in mice of a susceptible strain. Perhaps, age-related neoplastic changes might be exacerbated by long-lasting administration of high doses. Swiss albino mice with high background prevalence of malignant	**Animal data.** In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats. In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.	**Animal data.** EPA/OPP and EFSA concluded that all tumors were not treatment-related, based on lack of statistical significance, lack of dose-response, observations at only the highest dose, incidences within or close to historical control rates, no preneoplastic changes, or similar tumors were not observed in other studies. EPA/OPP and EFSA focus on pairwise comparisons (which were generally not significant), while IARC also uses trend tests

showed a significant increase in the incidence of pancreatic islet cell adenoma in males – one of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site. One study in Wistar rats was inadequate for the evaluation because of the short duration of exposure. In the study in Wistar rats given drinking-water containing glyphosate, there was no significant increase in tumour incidence. A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation–promotion study in male Swiss mice. The study of a glyphosate-based formulation in drinking-water in Sprague-Dawley rats was inadequate for the evaluation because of the small number of animals per group, and the limited information provided on tumour histopathology and incidence in individual animals. These studies of a chemical mixture containing glyphosate were considered inadequate to evaluate the carcinogenicity of glyphosate alone. **<u>Evaluation:</u>** **Sufficient evidence ←** Limited evidence Inadequate evidence Evidence suggesting lack of carcinog'icity	lymphoma could be more vulnerable than other strains. Since the more frequent occurrence of malignant lymphoma was confined to a very high dose level that was administered over a long period, glyphosate was is considered unlikely to pose a carcinogenic risk in humans. Classification and labelling for carcinogenicity is not considered appropriate by the RMS because of the following considerations: (1) The presumed effect was observed in only one of five long-term studies in mice in a strain with a rather high background incidence of malignant lymphoma. Taking into account the huge amount of information on historical control incidences, there was no evidence of a similar effect in any other study. (2) Although the increase in lymphoma incidence in the study by (2001, ASB2012-11491) was statistically significant in both sexes, it was still within the (small) historical control range of the performing laboratory for females. No evidence of a similar effect in female mice was obtained in any other study. (3) No evidence of carcinogenicity was obtained in a total of six valid 2-yr studies in rats (see above) in which sufficiently high dose levels were employed. (4) The dose with a significantly higher lymphoma incidence (1460 mg/kg bw/day) is by more 2900 times higher than the proposed ADI and the margin to the expected consumer exposure is even wider. (5) There is no convincing evidence of carcinogenicity of glyphosate in humans coming from the epidemiological studies (see below). [German report, p 65]		(which yielded several significant results). In a few cases, EPA/OPP reported trend test results that differed from those of IARC but did not report which test they used. The EPA's cancer guidelines state, "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result." The German report (Oct 2015) discusses results of an 18-month study from 2001 in swiss albino mice fed glyphosate at doses of 0, 500, 1500, and 5000 ppm. Malignant lymphomas were observed in 10/50, 15/50, 16/50, and 19/50 males and in 18/50, 20/50, 19/50, and 25/50 females, respectively. Pairwise comparisons for each highest dose are statistically significant. IARC (March 2015) did not evaluate this study, as limited data were provided in a publicly available review article. EFSA (Nov 2015) includes this study; EPA/OPP does not.
<u>Mechanistic data.</u> There is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. In-vivo studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow. The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage. Tests in bacterial		**<u>Mechanistic data.</u>** Glyphosate was not mutagenic in bacteria or mammalian cells in vitro. Additionally, glyphosate did not induce chromosomal aberrations in vitro. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. 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. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also	

assays gave consistently negative results. Strong evidence exists that glyphosate, AMPA, and glyphosate-based formulations can induce oxidative stress. Evidence came from studies in many rodent tissues in vivo, and human cells in vitro. In some of these studies, the mechanism was challenged by co-administration of antioxidants and observed amelioration of the effects. Similar findings have been reported in fish and other aquatic species. Various end-points (e.g. lipid peroxidation markers, oxidative DNA adducts, dysregulation of antioxidant enzymes) have been evaluated in numerous studies. This increased the confidence of the Working Group in the overall database. **Evaluation:** Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.		provides SAR support for the lack of mutagenic/genotoxic potential. IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (i.e., no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (e.g., comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (e.g. chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.	
Overall evaluation: Carcinogenic to humans **Probably carcinogenic to humans ←** Possibly carcinogenic to humans Not classifiable Probably not carcinogenic to humans	**Overall evaluation:** In the Pesticides Peer Review 125 expert meeting (February 2015), it was agreed that there is no need to propose classification and labelling of glyphosate for carcinogenicity. **Unlikely to be carcinogenic ←**	**Overall evaluation:** Carcinogenic to humans Likely to be carcinogenic to humans Suggestive evidence of carcinogenicity Inadequate information **Not likely to be carcinogenic ←**	See attached cancer descriptors from the EPA's cancer guidelines.