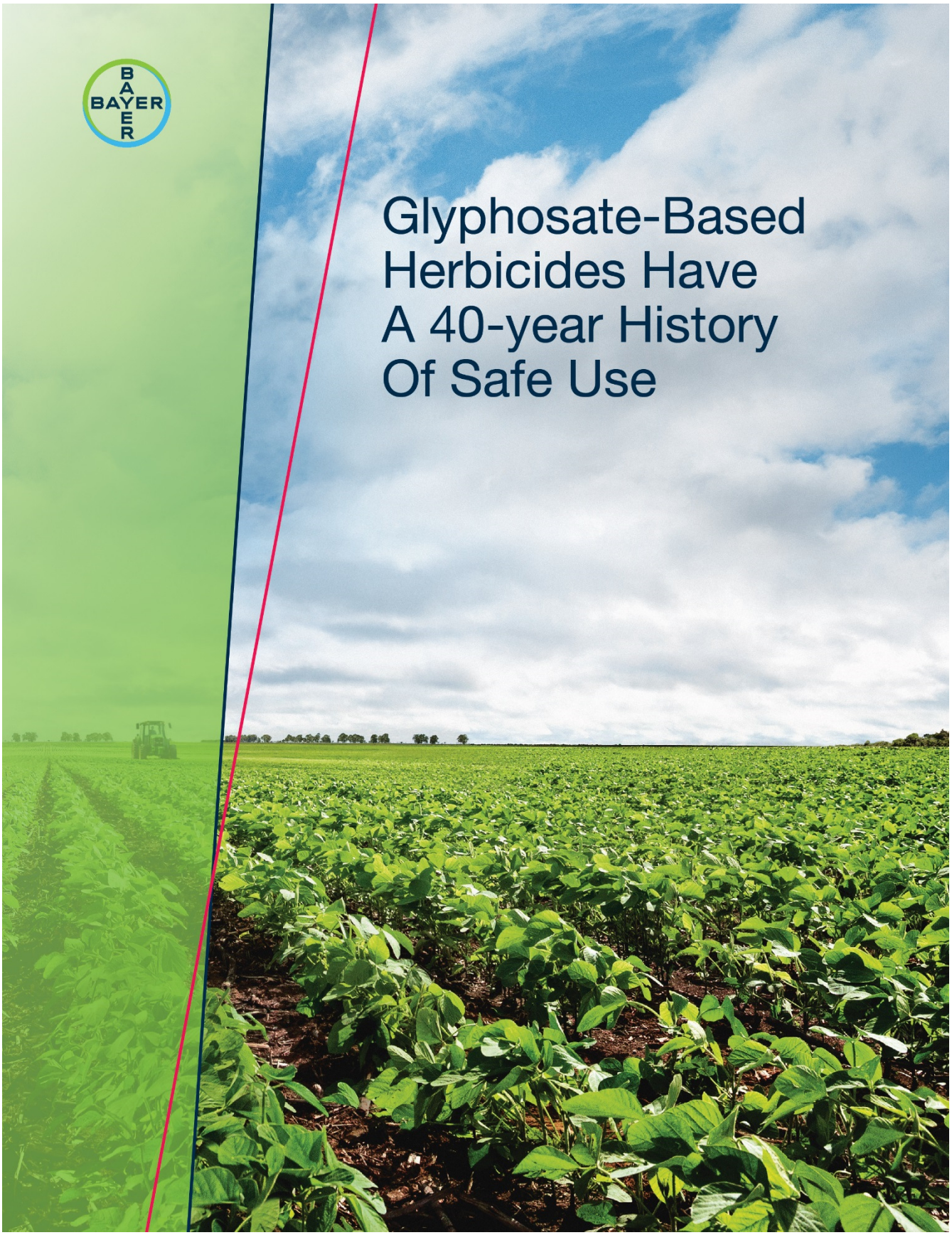
Glyphosate-Based Herbicides Have A 40-year History Of Safe Use



Introduction

For more than 40 years, farmers, governments, gardeners, and others have depended on glyphosate as an efficient and cost-effective tool that can be used safely to control problematic weeds. Since their introduction in 1974, glyphosate-based products have become the most commonly used herbicides in the world. This widespread adoption is based on three key factors:

- Glyphosate effectively controls a broad spectrum of troublesome weeds
- Glyphosate offers significant economic and environmental benefits
- Glyphosate has a strong safety profile and a long history of safe use

Glyphosate has been a breakthrough for farming. Not only do glyphosate products work well on weeds, but they also help farmers grow crops more sustainably. For example, glyphosate has helped farmers adopt what is called "conservation tillage." With conservation tillage, farmers can disturb less soil and drive their tractors less. Thus, farmers can reduce soil erosion and carbon emissions, which is great for the environment.

When it comes to safety assessments, no other pesticide has been more extensively tested than glyphosate. In evaluations spanning four decades, the overwhelming conclusion of experts worldwide has been that glyphosate, when used per label directions, does not present an unreasonable risk of adverse effects to humans, wildlife or the environment.

Like all pesticides, regulatory authorities around the world routinely review the latest safety data on glyphosate. With seven complete regulatory data packages from multiple registrants, glyphosate safety is supported by one of the most extensive worldwide human health, crop residue and environmental databases ever compiled on a pesticide product. The consensus of this comprehensive set of toxicology studies have consistently demonstrated that glyphosate has low oral, dermal, and inhalation toxicity, and shows no evidence of genotoxicity, neurotoxicity, immunotoxicity, disrupting the endocrine system, reproductive or developmental toxicity, and it does not produce malformations.

Regulatory authorities, scientific bodies, and independent scientists have consistently concluded that glyphosate does not pose a carcinogenic hazard to humans. The conclusions of leading regulators and agencies around the world, including the U.S. Environmental Protection Agency (EPA), European Food Safety Authorities (EFSA), European Chemicals Agency (ECHA), German BfR, and Australian, Canadian, Korean, New Zealand and Japanese regulatory authorities, as well as the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), continue to reaffirm that glyphosate is not carcinogenic. Most recently, in April 2019, the U.S. EPA stated that "EPA continues to find that there are no risks to public health when glyphosate is used in accordance with its current label and that glyphosate is not a carcinogen. The agency's scientific findings on human health risk are consistent with the conclusions of science reviews by many other countries and other federal agencies." Furthermore, in November 2017, the U.S. Agriculture Health Study, which is the largest study of the real-world use of pesticides and health risks, published new findings showing no connection between use of glyphosate-based herbicides and cancer.

As consumers ourselves, we fully support the comprehensive and science-based processes used by the regulatory authorities around the world to ensure glyphosate and other herbicides can be used safely.

Regulatory Reviews on Glyphosate since 2015

United States Environmental Protection Agency (US EPA, 2019)
In April of 2019, US EPA issued Proposed Interim Registration Review Decision for glyphosate and concluded that "The EPA thoroughly assessed risks to humans form exposure to glyphosate from all uses and all routes of exposure and did not identify any risks of concern. Both non-cancer and cancer effects were evaluated for glyphosate and its metabolites, aminomethyl phosphonic acid (AMPA) and N-acetyl-glyphosate." Summary of conclusion is provided below:

"Cancer Assessment
The EPA convened a FIFRA SAP meeting in December 2016 to consult on the carcinogenic potential of glyphosate. Recommendations from the Scientific Advisory Panel meeting were published in March 2017. The EPA revised its cancer assessment based on comments received from the SAP and responded to the SAP in the Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate. The EPA's final cancer conclusion and its rationale for reaching this conclusion is described in the Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. The EPA's final cancer assessment includes the newly published analysis of glyphosate use and cancer incidence in the Agricultural Health Study (AHS). The AHS study is a long-term epidemiological study of over 54 thousand pesticide applicators to investigate the association between pesticide exposures and incidence of various types of cancer and non-cancer outcomes. The EPA's review of the AHS study is described in the Summary Review of Recent Analysis of Glyphosate Use and Cancer Incidence in the Agricultural Health Study. The agency has determined that glyphosate is not likely to be carcinogenic to humans and therefore a quantitative cancer assessment was not conducted. All docurnents relating to the cancer evaluation for glyphosate are published in the public • registration review docket for glyphosate (EPA-HQ-OPP-2009-0361). The deliberations of the glyphosate FIFRA SAP meeting, including agenda, meeting notes, SAP recommendations, the EPA's presentation to the FIFRA SAP, and other supporting documents are published in the glyphosate FIFRA SAP docket (EPA-HQ-OPP-2016-0385) at 'vww.reeulations.eov"

As part of EPA's responses to comments received during the public commenting period, the agency addressed the IARC evaluation:

"EPA's cancer evaluation is more robust than IARC's evaluation. IARC's evaluation only considers data that have been published or accepted for publication in the openly available scientific literature. As a result, IARC only considered a subset of the studies included in the EPA's evaluation. For instance, IARC only considers 8 animal carcinogenicity studies while the agency used 15 acceptable carcinogenicity studies in its evaluation. The EPA also excluded some studies that were not appropriate for determining the human carcinogenic potential of glyphosate, such as studies in non-mammalian species (i.e., worms, fish, reptiles and plants) which IARC used in its evaluation.

The Agency's cancer evaluation for glyphosate is also more transparent. EPA's draft cancer evaluation was presented to a FIFRA SAP for external peer review. EPA solicited public comments on the carcinogenic potential of glyphosate as part of the SAP process, which is well-documented with an agenda, transcript, meeting notes, and final SAP report. EPA responded to the SAP report, addressed panel recommendations, and made revisions to its cancer assessment that were transparent and provided to the public. EPA also solicited public comments on its full human health and ecological risk assessment for glyphosate in February

2018. In contrast, IARC meetings are not accessible to public. Its deliberations are closed, its process does not allow for public comments to be submitted for consideration, there are no materials provided in advance of the meeting, and IARC's reports are final without an external peer review."

https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-2344

Brazilian Health Surveillance Agency (ANVISA, 2019)
In March of 2019, Anvisa issued a technical note on glyphosate and presented the conclusions of the reassessment that glyphosate does not have mutagenic, teratogenic, and carcinogenic characteristics, it is not an endocrine disruptor or toxic for reproduction. Summary of conclusion is provided below:
"Anvisa reassessed the active ingredient Glyphosate and concluded that, regarding the prohibitive registration properties provided for in Law 7.802 of July 1989, Glyphosate does not have mutagenic, teratogenic, and carcinogenic characteristics, it is not an endocrine disruptor or toxic for reproduction. There is no scientific evidence that Glyphosate causes more damage to health than tests on laboratory animals have shown. After assessing the scientific studies and reports of international regulatory agencies, Anvisa determined new benchmarks for the risk assessment of Glyphosate, namely: Acceptable Daily Intake (ADI) = 0.5 mg/Kg bw/day; Acute Reference Dose (ARfD) = 0.5 mg/kg bw/day; Acceptable Occupational Exposure Level (AOEL) = 0.1 mg/kg bw/day. Based on these parameters, the dietary risk assessment related to Glyphosate showed a safe level of exposure, with no extrapolation of the acute and chronic reference doses, including in this evaluation the residues found in food and water. International monitoring studies also show a lack of risk for dietary exposure, including for lactating mothers. The definition of residues has been changed. Glyphosate residues for compliance with the Maximum Residue Limit for all crops, including genetically modified CP4-EPSPS, will be established by the amount of Glyphosate. Glyphosate residues for dietary risk assessment should be expressed from the sum of glyphosate residues + AMPA for all crops, including genetically modified CP4-EPSPS. Regarding toxicologically relevant impurities, Anvisa maintains the maximum limit for N-nitrosoglyphosate at 0.001 g/kg, and has reduced the maximum formaldehyde limit to 1.0 mg/kg. The evaluation of toxicologically relevant components led to the proposal to prohibit products with a POEA concentration above 20% to ensure safe dietary exposure."

https://sei.anvisa.gov.br/autenticidade

Health Canada Pest Management Regulatory Agency (PMRA, 2019)
In January of 2019, PMRA issued the following statement on Glyphosate:

"Following the release of the Department's final re-evaluation decision on glyphosate in 2017, Health Canada received eight notices of objection. There have also been concerns raised publicly about the validity of some of the science around glyphosate in what is being referred to as the Monsanto Papers.

Health Canada scientists reviewed the information provided in these notices, and assessed the validity of any studies in question, to determine whether any of the issues raised would influence the results of the assessment and the associated regulatory decision.

After a thorough scientific review, we have concluded that the concerns raised by the objectors could not be scientifically supported when considering the entire body of relevant data. The objections raised did not create doubt or concern regarding the scientific basis for the 2017 re-evaluation decision for glyphosate. Therefore, the Department's final decision will stand.

Health Canada follows a transparent and rigorous science-based regulatory process when making decisions about the safety of pesticides. As part of this process, Health Canada will publish its response to each notice of objection in the Pest Management Regulatory Agency's Public Registry on January 14.

Our scientists left no stone unturned in conducting this review. They had access to all relevant data and information from federal and provincial governments, international regulatory agencies, published scientific reports and multiple pesticide manufacturers. This includes the reviews referred to in the Monsanto Papers. Health Canada also had access to numerous individual studies and raw scientific data during its assessment of glyphosate, including additional cancer and genotoxicity studies. To help ensure an unbiased assessment of the information, Health Canada selected a group of 20 of its own scientists who were not involved in the 2017 re-evaluation to evaluate the notices of objection.

No pesticide regulatory authority in the world currently considers glyphosate to be a cancer risk to humans at the levels at which humans are currently exposed. We continue to monitor for new information related to glyphosate, including regulatory actions from other governments, and will take appropriate action if risks of concern to human health or the environment are identified."

https://www.canada.ca/en/health-canada/news/2019/01/statement-from-health-canada-on-glyphosate.html

United States Environmental Protection Agency (US EPA, 2017)
In December of 2017, US EPA released draft risk assessments for glyphosate as part of the registration review that has been ongoing since 2009. Registration reviews occur routinely for all previously approved pesticides. The purpose of a registration review is to ensure registered pesticides continue to meet the FIFRA standard for registration. Summary of EPA's draft risk assessment conclusion is provided below:

"Hazard Characterization: Glyphosate exhibits low toxicity across species, durations, life stages, and routes of exposure. There were no effects observed in route-specific dermal and inhalation studies. There was no evidence that glyphosate is neurotoxic or immunotoxic."

"Glyphosate showed no evidence of increased quantitative or qualitative susceptibility following in utero exposures to rats or rabbits. In rats, maternal and developmental toxicity was observed only at or above the limit dose. In rabbits, maternal toxicity was comprised mainly of clinical signs (diarrhea, few and/or soft feces) and no developmental toxicity was observed. In one of the twogeneration rat reproductive toxicity studies, no adverse effects were seen in the parental animals including reproductive toxicity. While there was an increased postnatal quantitative susceptibility, offspring effects were observed only at the limit dose (1000 mg/kg/day) and consisted of delayed age and increased weight at attainment of preputial separation (PPS)."

“Glyphosate is categorized as having low acute toxicity for the oral, dermal, and inhalation routes (Toxicity Categories III or IV). It is a mild eye irritant (Toxicity Category III), slight skin irritant (Toxicity Category IV), and is not a dermal sensitizer.”

“Additionally, the Agency reevaluated the human carcinogenic potential of glyphosate, which included a weight-of-evidence evaluation of data from animal toxicity, genotoxicity, and epidemiological studies. This evaluation was presented to the Federal Insecticide, Fungicide, and Rodenticide Scientific Advisory Panel (FIFRA SAP) and was subsequently updated based on their review. The Agency concluded that glyphosate should be classified as “not likely to be carcinogenic to humans.”

“In response to concern from segments of the general public related to the presence of glyphosate in human milk, the EPA Biological and Economic Analysis Division Analytical Chemistry Branch (BEAD-ACB) analyzed human milk samples collected by the National Children’s Study for residues of glyphosate and the glyphosate metabolites N-acetyl-glyphosate and AMPA (aminomethyl phosphonic acid; see Attachment A for structures). A total of 39 samples from 39 mothers were analyzed. Glyphosate, N-acetyl-glyphosate, and AMPA were not detected in the samples (glyphosate limit of quantitation (LOQ)/limit of detection (LOD) = 10 ppb/3.3 ppb; metabolite LOQ/LOD = 30 ppb/10 ppb) (ACB Project #B14-46, L. Podhorniak, 13-May-2015).”

“Aggregate Risk Assessment: In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. Based on the registered/proposed agricultural and residential uses, HED conducted short-term (food, water, residential incidental oral) and chronic (food and water) aggregate risk assessments. The resulting aggregate risk estimates are all less than HED’s LOC. It is noted that the short-term assessment is protective of intermediate-term exposure as the relevant PODs for these durations are identical.”

“Occupational Risk Assessment: For glyphosate, based on the currently registered use patterns, there is a potential for short-term dermal and inhalation exposure to occupational handlers (mixing, loading, and applying) as well as short-term dermal and inhalation exposure from post-application activities. Since short- and intermediate-term dermal or inhalation endpoints were not selected, a quantitative exposure risk assessment was not completed for these routes of exposure.”

“Human Studies: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include the 2012 Residential SOPs (Lawn/Turf), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticidehandler”

https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0068

European Food and Safety Authority (EFSA, 2017)

In September of 2017, after comprehensive review of endocrine data set on glyphosate EFSA published its conclusion that glyphosate does not have oestrogen, androgen, thyroid and steroidogenesis (EATS)-mediated endocrine disrupting properties. Summary of conclusion is provided below:

"On 12 November 2015, the European Food Safety Authority (EFSA) published its Conclusion on thepeer review of the pesticide risk assessment of the active substance glyphosate in the framework of the renewal of the approval under Commission Regulation (EU) No 1141/2010 (EFSA Journal 2015;13(11):4302). Based on the assessment of the representative uses evaluated during the peer review, EFSA noted that for certain effects observed in one study at parental toxic doses, signs of endocrineactivity could not be completely ruled out and a data gap was identified. While pertinent data became available which could not be included in the renewal procedure, it was considered by the European Commission desirable to address this issue through a focussed scientific assessment.
On 27 September 2016, EFSA received a mandate from the European Commission to consider information on potential endocrine activity of glyphosate in accordance with Article 31 of Regulation (EC) No 178/2002. In particular, EFSA has been requested to assess the available information on potential endocrine activity of glyphosate, and conclude whether the data gap set in the EFSA Conclusion published on 12 November 2015 (EFSA Journal 2015;13(11):4302) is addressed.
On 4 October 2016, EFSA has requested relevant data related to potential endocrine activity of glyphosate from the applicant for the renewal of the approval of glyphosate, i.e. the Glyphosate Task Force. The initial assessment of the data submitted was carried out by the competent authority of the rapporteur Member State, Germany, in the format of an addendum to the renewal assessment report, which was received by EFSA on 31 March 2017. Subsequently, the addendum was distributed to Member States, the applicant and EFSA for comments on 3 April 2017. In addition, an expert consultation was conducted in the areas of mammalian toxicology and ecotoxicology. The current conclusion presents a follow-up assessment to the existing EFSA Conclusion on the peer review for the renewal of the approval of glyphosate (EFSA Journal 2015;13(11):4302) focused on the data gap identified in relation to the endocrine activity of the substance. The current assessment concluded that glyphosate does not have oestrogen, androgen, thyroid and steroidogenesis (EATS)-mediated endocrine disrupting properties based on the facts that no endocrinemediated adverse effects were identified in apical studies; the weak evidence seen in a limited number of supplementary in vitro studies was inconsistent with the findings of the acceptable OECD (Organisation for Economic Co-operation and Development) tests and it was not expressed in vivo in the OECD Level 4 and 5 studies; and no EATS-mediated endocrine mode of action was identified. Since the database available to reach this conclusion was quite comprehensive, it was concluded that the data gap identified in the previous EFSA conclusion (EFSA Journal 2015;13(11):4302) was adequately addressed. Glyphosate effects on reproductive parameters were observed in some ecotoxicology studies. However, these effects were not consistently observed and no indication was found that the effects are related to an androgenic, estrogenic, steroidogenic or thyroidal mode of action. No evidence was found in the available ecotoxicology studies which would contradict the conclusion of mammalian toxicology that there is no evidence of endocrine mode of action of glyphosate."

http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4979/pdf

Health Canada Pest Management Regulatory Agency (PMRA, 2017)

In April of 2017, after a comprehensive multi-year re-evaluation of glyphosate, PMRA granted continued registration of products containing the active ingredient glyphosate for sale and use in Canada. The re-evaluation process by regulatory agencies is standard and occurs on a regular basis for all registered pesticides ensuring that all registered pesticides continue to meet the stringent, modern standards for human health and environmental protection. Summary of conclusion is provided below:

"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."

http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rvd2017-01/index-eng.php

European Chemical Agency (ECHA, 2017)

In March of 2017, after a rigorous and comprehensive assessment of the safety data on glyphosate, the Risk Assessment Committee (RAC) of ECHA concluded that based on available scientific evidence, there should be no change to the current classification, wherein glyphosate is considered as non-carcinogenic, non-mutagenic, non-reprotoxic, non-genotoxic and without specific target organ toxicity. ECHA assesses whether the intrinsic properties of the active substance meet the hazard criteria set out in the Classification, Labeling and Packaging Regulations and evaluation does not include the risk of exposure.
Apart from the published studies on glyphosate, the review was based on full reports of studies conducted by the industry and together included more than 90,000 pages of data. This scientific evaluation in the EU was preceded by previous conclusions of non-carcinogenic classification of glyphosate by EFSA and BfR. Summary of RAC's conclusion is provided below:

"RAC concluded that the available scientific evidence did not meet the criteria in the CLP Regulation to classify glyphosate for specific target organ toxicity, or as a carcinogen, as a mutagen or for reproductive toxicity.

The hazard classes for which classification was proposed by the German competent authority were specific target organ toxicity (repeated exposure) (category 2), eye damage/irritation (category 1), and toxicity to the aquatic environment (Aquatic Chronic 2). ECHA also assessed other hazard classes including carcinogenicity, germ cell mutagenicity and reproductive toxicity."

https://echa.europa.eu/-/glyphosate-not-classified-as-a-carcinogen-by-echa

Korean Rural Development Administration (RDA, 2017)

In March of 2017, Korea RDA publicly announced its completion of safety re-evaluation of Glyphosate and removed previously implemented sale restrictions based on IARC's classification in 2015. RDA concluded based on animal studies and in alignment with large-scale epidemiological studies that there is no carcinogenic associations of glyphosate and humans. Below is the summary of the conclusions:

"The Rural Development Administration (RDA/Administrator CHUNG Hwang-keun) states that the RDA has finished the safety re-evaluation on glyphosate, diazinon and malathion, which the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO) announced as probable carcinogens in March 2015, and that the RDA has completed required actions on February 28, 2017.

Glyphosate and diazinon were re-assessed based on the WHO and the U.S. evaluation document alongside results from in-country exposure assessment on farmers. With the evaluation completed, restrictions on new and revised registration of glyphosate and diazinon as well as the sales cap were lifted as of February 2nd 2017.

Safety re-evaluation concluded that since glyphosate is a nonselective herbicide only used on weeds and not on crops in Korea, the possibility of dietary exposure through agricultural products was negligible. Moreover, it was concluded that animal testing found no carcinogenic association and health risk of glyphosate on farmers was low. Likewise, diazinon did not lead to

cancer in animal testing and its genetic toxicities were established to be negative. The substance also posed little health risk to farmers.

The European Food Safety Authority (November 2015), Food Safety Commission of Japan (March 2016), Joint FAO/WHO Meeting on Pesticide Residues (May 2016), and the U.S. Environment Protection Agency (September 2016) have all assessed glyphosate as non-carcinogenic pesticide.

Although glyphosate is used as a desiccant before harvesting wheat and barley in the U.S. and Europe, carcinogenic correlation was either low or non-existent. A large-scale of epidemiological studies on glyphosate similarly found no cancer link. Diazinon was also concluded to have neither carcinogenicity nor genetic toxicity.

Despite confirming the safety of these pesticides through safety re-evaluation, RDA urged farmers to comply with the safety standards and guidelines. Farmers should wear protective gear including protective clothing and mask when handling pesticides and observe standards for safe usage to protect their health and agricultural products.

“Going forward, we continue ramping up pesticide safety control in pesticide registration to safeguard people and environment and boosting safe agricultural production” said the RDA’s Director of the Agro-material Industry Division, KIM Kyung-sun.”

http://www.rda.go.kr/board/board.do?mode=view&prgId=day_farmprmninfoEntry&dataNo=100000731828

Australian Pesticides and Veterinary Medicines Authority (APVMA, 2016)

In September of 2016, APVMA concluded the re-assessment process for glyphosate that was initiated following the classification of glyphosate as a probable human carcinogen by the IARC. The APVMA’s evaluation methodology and regulatory conclusions summary is provided below:

“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-ofevidence 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). “

“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.”

https://apvma.gov.au/sites/default/files/publication/20701-glyphosate-regulatory-position-report-final.pdf

US Environmental Protection Agency (US EPA, 2016)

in September of 2016, EPA re-affirmed their position of glyphosate not likely to be carcinogenic to humans in the Glyphosate Issue Paper. Summary of conclusion is provided below:

“Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. Following the introduction of glyphosate-resistant crops in 1996, glyphosate use increased dramatically; however, glyphosate use has stabilized in recent years due to the increasing number of glyphosate-resistant weed species.

Since its registration in 1974, numerous human and environmental health analyses have been completed for glyphosate, which consider all anticipated exposure pathways. Glyphosate is currently undergoing Registration Review. As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health using current practices and policies. The human carcinogenic potential of glyphosate has been evaluated by the agency several times. As part of the current evaluation for Registration Review, the agency has performed a comprehensive analysis of available data from submitted guideline studies and the open literature. This includes epidemiological, animal carcinogenicity, and genotoxicity studies.

An extensive database exists for evaluating the carcinogenic potential of glyphosate, including 23 epidemiological studies, 15 animal carcinogenicity studies, and nearly 90 genotoxicity

studies for the active ingredient glyphosate. These studies were evaluated for quality and results were analyzed across studies within each line of evidence. The modified Bradford Hill criteria were then used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance and biological plausibility. The available data at this time do no support a carcinogenic process for glyphosate. Overall, animal carcinogenicity and genotoxicity studies were remarkably consistent and did not demonstrate a clear association between glyphosate exposure and outcomes of interest related to carcinogenic potential. In epidemiological studies, there was no evidence of an association between glyphosate exposure and numerous cancer outcomes; however, due to conflicting results and various limitations identified in studies investigating NHL, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. Increases in tumor incidence were not considered treatment-related in any of the animal carcinogenicity studies. In 7 of these studies, no tumors were identified for detailed evaluation. In the remaining studies, tumor incidences were not increased at doses < 500 mg/kg/day, except for the testicular tumors observed in a single study. Increased tumor incidences at or exceeding the limit dose (≥1000 mg/kg/day) are not considered relevant to human health. Furthermore, data from epidemiological and animal carcinogenicity studies do not reliably demonstrate expected dose-response relationships.

For cancer descriptors, the available data and weight-of-evidence clearly do not support the descriptors “carcinogenic to humans”, “likely to be carcinogenic to humans”, or “inadequate information to assess carcinogenic potential”. For the “suggestive evidence of carcinogenic potential” descriptor, considerations could be looked at in isolation; however, following a thorough integrative weight-of-evidence evaluation of the available data, the database would not support this cancer descriptor. The strongest support is for “not likely to be carcinogenic to humans” at doses relevant to human health risk assessment.
This analysis integrating multiple lines of evidence highlights the need for mechanistic studies to elucidate the MOA/AOP of glyphosate, as well as additional epidemiology studies and updates from the AHS cohort study to further investigate the carcinogenic potential of glyphosate in humans. This evaluation focused on studies on the active ingredient glyphosate; however, additional research could also be performed to determine whether formulation components, such as surfactants, influence the toxicity of glyphosate formulations.

The agency has been working on plans to initiate research given these identified data gaps and these plans are described in Section 7.0. The agency is soliciting advice from the FIFRA SAP on the evaluation and interpretation of the available data for each line of evidence for the active ingredient glyphosate and the weight-ofevidence analysis, as well as how the available data inform cancer classification descriptors according to the agency’s 2005 Guidelines for Carcinogen Risk Assessment.

https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0094

New Zealand Environmental Protection Agency (NZ EPA, 2016)

In August of 2016, NZ EPA conducted a review of the evidence relating to glyphosate and carcinogenicity and concluded that glyphosate is unlikely to be genotoxic or carcinogenic. Summary of conclusions is provided below:

“The review concluded that glyphosate is unlikely to be carcinogenic to humans or genotoxic (damaging to genetic material or DNA) and should not be classified as a mutagen or carcinogen under the HSNO Act.

This conclusion was based largely on consideration of the results of studies on humans (epidemiology studies) and studies in laboratory animals, as well as genotoxicity studies conducted by a range of methods. More details are provided below.

Studies on humans
The majority of human studies did not show an association between exposure to glyphosate and cancer. Although a small number of studies with a limited number of participants found a weak association between glyphosate exposure and increased risk of non-Hodgkin lymphoma (NHL), other studies did not. The studies that found no association between glyphosate exposure and NHL included the largest and most reliable study, which included over 50,000 participants.
There were also a number of limitations to many of the studies. These included only a small number of people being assessed, people also being exposed to other pesticides, and methodological limitations with how the amount of glyphosate people were exposed to was measured.
Based on the inconsistency in the results of the studies on glyphosate exposure and NHL, and the lack of any association in the largest, most robust study, it was concluded that there is no convincing evidence of an association between glyphosate exposure and the development of cancer in humans.

Studies in laboratory animals
A small number of studies in laboratory animals found an increased incidence of cancers in rats or mice exposed to glyphosate. However, these findings were not considered to be reliable evidence of a carcinogenic effect by overseas regulators for a number of reasons including:

- There was a lack of dose response. Normally the incidence or severity of toxicological effects caused by chemicals increases as the amount of exposure to the chemical increases. This was not seen in the studies with glyphosate.
- In most cases tumours occurred only at very high doses which were at or above recommended maximum doses for animal studies so are not considered relevant for humans.
- The incidences of cancers in most studies were within the range of normal incidences of these cancers in the test animals.
- The carcinogenic effects seen in a small number of studies were not seen in other studies conducted in the same species at the same dose levels.

Therefore Dr Temple concluded that the overall weight of evidence indicates that glyphosate is not carcinogenic.

Genotoxicity studies
All studies done according to internationally agreed test guidelines did not find evidence of a genotoxic (damaging to DNA) effect of glyphosate. Some studies with pesticide formulations that contain glyphosate showed a genotoxic effect. However, in some cases these studies were conducted in test systems that have not been validated as relevant to assess genotoxicity. In addition, because genotoxic effects were not seen with glyphosate itself, it is possible that the effects were related to other components in the formulations that were tested.
It was concluded that the weight of evidence indicates that glyphosate is not genotoxic.

http://www.epa.govt.nz/Publications/EPA_glyphosate_review.pdf

Joint United Nations Food and Agricultural Organization and WHO Meeting on Pesticide Residues (JMPR, 2016)

In May of 2016, JMPR re-evaluated glyphosate and concluded that the substance is unlikely to pose a carcinogenic risk to humans from exposure through the diet. The full conclusions from JMPR are provided below:

"Glyphosate is a broad-spectrum systemic herbicide. Several epidemiological studies on cancer outcomes following occupational exposure to glyphosate were available. The evaluation of these studies focused on the occurrence of NHL. Overall, there is some evidence of a positive association between glyphosate exposure and risk of NHL from the case–control studies and the overall metaanalysis. However, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. Glyphosate has been extensively tested for genotoxic effects using a variety of tests in a wide range of organisms. The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg body weight by the oral route, the route most relevant to human dietary exposure, was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans. The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures. Several carcinogenicity studies in mice and rats are available. The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet. The Meeting reaffirmed the group ADI for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an ARfD for glyphosate or its metabolites in view of its low acute toxicity."

http://www.who.int/foodsafety/jmprsummary2016.pdf?ua=1

Japan Food Safety Commission (FSC, 2016)

In March of 2016, Food Safety Commission in Japan reviewed glyphosate acceptable daily intake and concluded that no neurotoxicity, carcinogenicity, reproductive effect, teratogenicity or genotoxicity was observed. The full conclusions from FSCJ are provided below:

"The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of glyphosate (CAS No. 1071-83-6), an amino acid herbicide, based on results from various studies. Several technical grades of glyphosate are currently available in Japan. Five-distinct assessment data sets were submitted from each manufacturer. Toxicological profiles were found to be largely consistent among them after the verification individually. The summary of the risk assessment of each technical grade of glyphosate (Glyphosate I to V) is shown in Appendix. The active ingredient of glyphosate is distributed various salt form such as glyphosate ammonium salt

(CAS No. 40465-66-5), glyphosate isopropylamine salt (CAS No. 38641-94-0) and glyphosate potassium salt (CAS No. 70901-121). Those salts are soluble in water. Whatever salt are applied to crops, the residue on the crops exists in the form of free acid. FSCJ established the unified acceptable daily intake (ADI) and acute reference dose (ARfD) of glyphosate through compiling these assessment results. In general, 14C-glyphosate orally administrated rapidly reached to the Cmax value in plasma and then was eliminated in rats. At least 20% of the radioactivity was absorbed and excreted efficiently in feces. Unchanged glyphosate and aminomethyl phosphonic acid (AMPA) were found in urine and feces.

The fates of 14C-glyphosate in livestock (goats and chicken) were also examined. Unchanged glyphosate was found as the major radioactive substance in urine, feces, organs and tissues, and AMPA was also found as the minor component. On the fate of 14C-glyphosate, and isopropylamine, potassium, trimesium or sodium salt of 14C-glyphosate in plants, AMPA was found more than 10% of the total radioactive residue (TRR). N-Acetylglyphosate and N-acetyl-AMPA were detected in the glyphosate tolerant soybean and corn as more than 10% of TRR. Major adverse effects of glyphosate were observed on reduced gain of body weight, GI tract (diarrhea, increased cecum weight, bowel dilatation, thickening of intestinal mucosa), and liver (increased alkaline phosphatase (ALP), hepatocellular hypertrophy). Glyphosate had no neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity. Among no-observed-adverse-effect levels (NOAELs) of each technical grade of glyphosate, the lowest value was 75 mg/kg bw/day on Glyphosate I derived from the maternal effects in the developmental toxicity study of rabbits. FSCJ, however, recognized it appropriate to set 100 mg/kg bw/day as the overall NOAEL in the developmental toxicity studies of rabbits, considering the dose settings and the toxicological effects observed in the four other corresponding studies. As the whole, the lowest value among NOAELs was 100 mg/kg bw/day obtained in the 90-days and one-year toxicity studies in dogs, and in the developmental toxicity studies of rabbits. FSCJ thus established an ADI for glyphosate at 1 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. The lowest NOAEL for adverse effects elicited by a single oral administration of glyphosate was 1,000 mg/kg bw observed in an acute toxicity studies in rats and mice. It is thus unnecessary to specify an ARfD, due to the exceeding of the cut off level (500 mg/kg bw). In plants, AMPA, N-acetyl-AMPA, and N-Acetylglyphosate were observed as exceeded 10% of TRR. N-acetylAMPA and N-Acetylglyphosate were not detected in rats. N-acetyl-AMPA had a very low acute toxicity (LD50 was beyond 5,000 mg/kg bw), and no genotoxicity. Thus the residue definition for the dietary risk assessment was identified to be glyphosate and N-Acetylglyphosate in agricultural products, and glyphosate (parent compound only) in livestock products.

http://www.fsc.go.jp/english/evaluationreports/agrichemicalsl_e1.html

European Food Safety Authority (EFSA, 2015)

In November of 2015, EFSA issued Renewal Assessment Report concluding that glyphosate is not classified or proposed to be classified as carcinogenic. Further details and summary conclusions are provide below:

"EFSA and the EU Member States have finalised the re-assessment of glyphosate, a chemical that is used widely in pesticides. The report concludes that glyphosate is unlikely to pose a carcinogenic hazard to humans and proposes a new safety measure that will tighten the control of glyphosate residues in food. The conclusion will be used by the European Commission in deciding whether or not to keep glyphosate on the EU list of approved active substances, and by EU Member States to re-assess the safety of pesticide products containing glyphosate that are used in their territories.

A peer review expert group made up of EFSA scientists and representatives from risk assessment bodies in EU Member States has set an acute reference dose (ARfD) for glyphosate of 0.5 mg per kg of body weight, the first time such an exposure threshold has been applied to the substance.

Jose Tarazona, head of EFSA's Pesticides Unit, said: "This has been an exhaustive process – a full assessment that has taken into account a wealth of new studies and data. By introducing an acute reference dose we are further tightening the way potential risks from glyphosate will be assessed in the future. Regarding carcinogenicity, it is unlikely that this substance is carcinogenic."

Unlikely to be carcinogenic

The peer review group concluded that glyphosate is unlikely to be genotoxic (i.e. damaging to DNA) or to pose a carcinogenic threat to humans. Glyphosate is not proposed to be classified as carcinogenic under the EU regulation for classification, labelling and packaging of chemical substances. In particular, all the Member State experts but one agreed that neither the epidemiological data (i.e. on humans) nor the evidence from animal studies demonstrated causality between exposure to glyphosate and the development of cancer in humans.

EFSA also considered, at the request of the European Commission, the report published by the International Agency for Research on Cancer (IARC), which classified glyphosate as probably carcinogenic to humans.

The evaluation considered a large body of evidence, including a number of studies not assessed by the IARC which is one of the reasons for reaching different conclusions.

As well as introducing the ARfD, the review proposed other toxicological safety thresholds to guide risk assessors: the acceptable operator exposure level (AOEL) was set at 0.1 mg/kg body weight per day and an acceptable daily intake (ADI) for consumers was set in line with the ARfD at 0.5 mg/kg body weight per day.

Dr Tarazona added that EFSA will use the new toxicological values during its review of the maximum residue levels for glyphosate in food, which will be carried out in cooperation with Member States in 2016."

http://www.efsa.europa.eu/en/press/news/151112

United States Environmental Protection Agency (US EPA, 2015)

In September 2015, a third review was done by the Cancer Assessment Review Committee (CARC). Relevant glyphosate data available to EPA at that time for glyphosate were reevaluated, including studies submitted by the registrant and studies published in the open literature.

"In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of- evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- 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 the following 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 and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. 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 seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, 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 four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear doseresponse relationship, were not supported pre-neoplastic changes (e.g., foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both in vitro and in vivo including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no in vivo genotoxic or mutagenic concern for glyphosate."

https://www.acsh.org/wp-content/uploads/2016/05/EPA-glyphosate-document-final.pdf

United States Environmental Protection Agency (US EPA, 2015)

In June of 2015, US EPA completed their endocrine disruption weight of evidence assessment on glyphosate and concluded that that glyphosate does not have endocrine disrupting

properties and there is no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways. Summary of conclusion is provided below:
"The Endocrine Disruptor Screening Programs (EDSP) Tier 1 assay battery is designed to provide the necessary empirical data to evaluate the potential of chemicals to interact with the estrogen (E), androgen (A) or thyroid (T) signaling pathways. This interaction includes agonism and antagonism at the estrogen and androgen receptors, altered steroidogenesis, as well as hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary thyroid (HPT) axes. In addition to the available Tier 1 assay data, other scientifically relevant information (OSRI), including general toxicity data and open literature studies of sufficient quality, were considered in this weight of evidence (WoE) assessment.

In determining whether glyphosate interacts with E, A or T hormone pathways, the number and type of effects induced, the magnitude of responses, and the pattern of responses observed across studies, taxa, and sexes were considered. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in general systemic toxicity or overt toxicity.

On September 17, 2014, the EDSP Tier 1 Assay Weight of Evidence Review Committee (T1WoERC) of the Office of Pesticide Programs (OPP) and the Office of Science Coordination and Policy (OSCP) conducted a weight-of-evidence (WoE) analysis of the potential interaction of glyphosate with the E, A or T hormone pathways. The T1WoERC conclusions from the WoE evaluation in this report are presented by pathway (E, A and then T) beginning with the results of the Tier 1 in vitro assays followed by in vivo mammalian and wildlife results, then the results of the cited OSRI for mammalian and wildlife studies (40 CFR Part 158 and literature).

For the estrogen pathway, while glyphosate showed estrogen receptor (ER) antagonism in vitro with estrogen-dependent human breast cancer cells (Thongprakaisang et al., 2013), there was no evidence of potential interaction of glyphosate with the estrogen pathway in the EDSP Tier 1 in vitro assays [i.e, ER binding, ER transactivation assay (ERTA), aromatase and steroidogenesis assays]. Additionally, glyphosate was negative in the Tier 1 in vivo mammalian assays (i.e., uterotrophic or female pubertal assays). In the fish short-term reproduction assay (FSTRA), the non-treatment-responsive decrease [only significant at mid-treatment] in vitellogenin (VTG) was seen in isolation in the absence of any treatment-related effects in the other estrogen-related endpoints such as gonado-somatic index (GSI), gonadal staging, fecundity and fertilization. In addition, there were no notable gonadal histopathology. There were no treatment-related effects on female reproductive parameters in the existing glyphosate Part 158 mammalian or wildlife studies (decreases in offspring body weight observed in one avian reproduction study). Therefore, there is no convincing evidence of a potential interaction with the estrogen pathway for glyphosate.

For the androgen pathway, there was no evidence of interaction of glyphosate with the androgen pathway in the Tier 1 in vitro [i.e, androgen receptor (AR) binding and steriodogenesis assays were negative] or Tier 1 in vivo FSTRA and mammalian assays (i.e., Hershberger and male pubertal assays were negative in the absence of overt toxicity). In addition, glyphosate was negative in an AR transactivation assay (Kojima et al., 2004). The only treatment-related effects observed in the Part 158 mammalian studies in the absence of overt toxicity were

decreases in sperm count in the subchronic rat study (1678 mg/kg/day) and a delay in preputial separation (PPS)at 1234 mg/kg/day in the post-1998 two-generation reproduction study in rats (the EDSP Tier 2 study). Both effects were observed at a dose that was above the limit dose (1000 mg/kg/day) for those studies. No androgen-related effects were seen in the wildlife Part 158 studies (decreases in offspring body weight observed in one avian reproduction study).

For the thyroid pathway, there was no convincing evidence of potential interaction of glyphosate. There were no treatment-related effects on thyroid hormones (T4 and TSH), thyroid weights or thyroid histopathology in the male pubertal assay in the absence of overt toxicity. There were no thyroid-related effects observed in the female pubertal assay. In the amphibian metamorphosis assay (AMA), there were no developmental effects or alterations in thyroid histopathology. No thyroid-related effects were noted in any of the Part 158 studies.

Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for glyphosate since there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways."

https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0047