UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: December 12, 2017

Subject: **Glyphosate.** Draft Human Health Risk Assessment in Support of Registration Review.

PC Codes: 417300; 103601; 103603; 103604; 103605; 103607; 103608; 103613;	**DP Barcode:** D417700
Decision No.: 487242	**Registration Nos.:** multiple
Petition No.: not applicable	**Regulatory Action:** Registration Review
Risk Assessment Type: Single Chemical Aggregate	**Case No.:** 178
TXR No.: NA	**CAS No.:** 1071-83-6; 38641-94-0; 70393-85-0; 114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1
MRID No.: NA	**40 CFR:** 180.364

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The Office of Pesticide Programs (OPP) HED assesses the risks posed to humans from exposure to pesticide chemicals. The PRD of OPP asked HED to evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered uses for glyphosate (*N*-(phosphonomethyl)glycine) in support of Registration Review. The human health risk assessment was provided by Monique Perron, the hazard characterization by Anwar Dunbar and Monique Perron, the residue chemistry review and dietary exposure assessment by Tom Bloem, the occupational/residential exposure assessments were by Lata Venkateshwara, and the drinking water assessment by James Hetrick of the Environmental Fate and Effects Division (EFED).

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1.0 EXECUTIVE SUMMARY

Background: Glyphosate is a nonselective Group 9 herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Glyphosate is also currently registered on turf (including golf courses and residential lawns) and on aquatic application scenarios. Tolerances are established for residues of glyphosate in/on numerous plant commodities at 0.2-400 ppm (40 CFR §180.364(a)) and for the combined residues of glyphosate and *N*-acetyl-glyphosate (expressed as glyphosate) in/on field corn, soybean, canola, aspirated grain fractions (AGF), and livestock commodities at 0.1-310 ppm. The Glyphosate Reregistration Eligibility Decision (RED) document was issued September 1993. HED completed a human health risk assessment scoping document in support of Registration Review on 3-June-2009 (D362745, J. Van Alstine *et al.*) and responded to public comments concerning this assessment on 28-Dec-2009 (D369999, J. Van Alstine *et al.*). The most recent human health risk assessment was completed on 14-November-2012 (D398547, T. Bloem *et al.*).

Hazard Characterization: Glyphosate exhibits low toxicity across species, durations, life stages, and routes of exposure. In most of the studies in its hazard database, effects are seen at doses at or above the limit dose (>1000 mg/kg/day). The observed effects included: decreases in body weights and minor indicators of toxicity to the eyes, liver, and/or kidney. 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 two-generation 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.

As part of Registration Review, the Agency collaborated with Health Canada's Pest Management Regulatory Agency (PMRA) to conduct an open literature review in 2012. A subsequent search of the open literature was conducted more recently by the Agency to supplement the joint review with PMRA. The only studies found to be appropriate for quantitative use identified no-observed adverse-effect levels (NOAELs) at doses well above the points of departure (PODs) currently used for risk assessment. As a result, there was no impact on the hazard characterization or draft human health risk assessment for glyphosate from open literature studies (TXR No. 0056885).

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."

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The developmental rabbit study was selected to evaluate chronic dietary and incidental oral exposures (NOAEL = 100 mg/kg/day). A total uncertainty factor of 100X (10X interspecies, 10X intraspecies and 1X FQPA SF) was applied to these exposures scenarios. An acute dietary endpoint was not selected since there were no effects observed in the database attributable to a single dose. Dermal and inhalation endpoints were not selected since there was no toxicity observed in route-specific toxicity studies and there was no concern for increased quantitative susceptibility to offspring.

Food Quality Protection Act (FQPA) Safety Factor (SF): The Agency recommends the FQPA SF be reduced to 1x. This recommendation is based on the following considerations: (1) the toxicological database for glyphosate is complete ; (2) there is no evidence of quantitative or qualitative fetal susceptibility in rats or rabbits following *in utero* exposure in the developmental studies; (3) there is no evidence of neurotoxicity in the glyphosate database, including the neurotoxicity battery; (4) the offspring effects in one of the two-generation reproductive toxicity studies (delayed age and increased weight at attainment of PPS) occurred at the limit dose with a clear NOAEL and the PODs used for risk assessment are protective of the observed offspring effects; and (5) the dietary and residential exposure analyses are conservative and do not underestimate exposure.

Dietary (food and water) Risk Assessment: A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID ver. 3.16) which incorporates consumption data from United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA; 2003-2008). Acute and cancer dietary risk assessments were not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup and glyphosate is classified as not likely to be a human carcinogen. The chronic analysis assumed tolerance-level residues, 100% crop treated, DEEM (ver. 7.81) default processing factors, and modeled drinking water estimates (direct application to water scenario). The resulting chronic risk estimates (food and water) were <100% of the chronic population-adjusted dose (cPAD) and are therefore less than HED's level of concern (children 1-2 years old were the most highly exposed population subgroup at 23% the cPAD).

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).

Residential and Non-Occupational Exposure and Risk Assessment: Residential exposure to glyphosate may occur as a result of the currently registered turf (including golf courses and residential lawns) and aquatic application scenarios. An updated residential exposure assessment was conducted to reflect HED's 2012 Residential Standard Operating Procedures (SOPs), policy changes for body-weight assumptions, updated POD, and updates to HED's inputs for aquatic/swimmer assessments.

Based on the registered turf and aquatic use patterns, there is a potential for short-term dermal and inhalation exposure to residential handlers (mixing, loading, and applying) and short-term dermal, inhalation, and incidental oral exposure from post-application activities. Since short- and intermediate-term dermal or inhalation PODs were not selected, a quantitative exposure and risk assessment was not completed for these routes of exposure. However, children may have short-term post-application incidental oral exposures from hand-to-mouth behavior on treated lawns and swimmers (adult and children) may have short-term post-application incidental oral exposures from aquatic uses. The resulting margins of exposure (MOEs) do not exceed HED's level of concern (LOC). It is noted that the short-term assessment is protective of intermediate-term exposure as the incidental oral PODs for these durations are identical.

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-pesticide-handler-exposure-data).

2.0 HED Conclusions

No data deficiencies were identified in the toxicological, residue chemistry, or occupational/residential exposure databases. In addition, the aggregate (food, water, and residential) risk assessments resulted in exposures less than HED's LOC (occupational exposure assessment is unnecessary; see above). HED notes that several crop groups have been updated since tolerances for residues of glyphosate were originally established. A summary of tolerance updates to align established glyphosate tolerances with the updated crop groups is provided in Section 2.2.2. As described in Section 2.3, this assessment assumes that all glyphosate labels are consistent with the uses described in the use summary submitted by the Joint Glyphosate Task Force. Provided the tolerance (see Section 2.2.2) and label (see Section 2.3) issues are addressed and standards are submitted to the National Pesticide Repository as indicated in the next paragraph, HED concludes that the human health risk assessment supports continuation of the current registered glyphosate uses.

The following standards should be submitted to the address specified below (extended zip code must be used): glyphosate, *N*-acetyl-glyphosate, glyphosate internal standard (2-^{13}C and ^{15}N; 3-^{13}C and ^{15}N).

USEPA - Thuy Nguyen
National Pesticide Standards Repository
701 Mapes Road
Fort Meade, MD 20755-5350

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate methods are available to enforce the currently established crop and livestock tolerances.

2.2.2 Recommended Tolerances

HED evaluated the glyphosate residue chemistry database to determine if the established tolerances conform to the current practices and to determine if the crop group/subgroup tolerances could be updated to the current crop group/subgroup definitions. Based on this analysis, HED is recommending for establishment of the tolerances listed in Attachment C Table C.1. With the establishment of these tolerances, the following tolerances should be deleted: acerola; aloe vera; ambarella; asparagus; atemoya; avocado; bamboo, shoots; banana; biriba; breadfruit; cactus, fruit; cactus, pads; canistel; cherimoya; custard apple; date, dried fruit; durian; feijoa; fig; fruit, stone, group 12; guava; ilama; imbe; imbu; jaboticaba; jackfruit; longan; lychee; mamey apple; mango; mangosteen; marmaladebox; noni; nut, tree, group 14; olive; palm heart; papaya; papaya, mountain; passionfruit; pawpaw; persimmon; pineapple; pistachio; pomegranate; pulasan; rambutan; rose apple; sapodilla; sapote, black; sapote, mamey; sapote, white; soursop; Spanish lime; star apple; starfruit; sugar apple; Surinam cherry; tamarind; vegetable, leafy, brassica, group 5; vegetable, leafy, except brassica, group 4; watercress, upland; and wax jambu.

2.2.3 International Harmonization

Attachment C includes a summary of the currently established U.S. glyphosate tolerances and the Codex and Canadian maximum residue limits (MRLs). As indicated in the attachment, since the U.S. and Canadian residue definitions differ, harmonization of the tolerance value is not feasible. The U.S. and Codex residue definitions are identical; however, harmonization is not appropriate as either the available residue data for the registered uses of glyphosate show residues higher than the Codex MRL or the Codex MRL is too high to be a measure of misuse.

2.3 Label Recommendations

As part of Registration Review, the Joint Glyphosate Task Force (JGTF) provided information concerning the labeled application scenarios for the following products (see Docket EPA-HQ-OPP-2009-0361): EPA Reg. Nos.: 100-1182, 228-713, 524-343, 524-475, 524-537, 524-549, 524-579, 4787-23, and 62719-556. HED notes that there are additional registered products and that the labeled instructions for these products should be consistent with the application scenarios summarized by the JGTF. HED notes that all labels should specify the following rotational crop restrictions: treated fields may be rotated to a labeled crop at any time and may be rotated to a non-labeled crop 30 days after application.

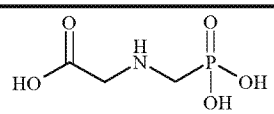
3.0 Introduction

Glyphosate is a non-selective herbicide that acts by blocking the activity of the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme, which is involved in the synthesis of the amino acids tyrosine, tryptophan, and phenylalanine.

3.1 Chemical Identity

The chemical structure and nomenclature for glyphosate are presented in Table 3.1. Attachment D provides a summary of the physicochemical properties of technical grade glyphosate.

Table 3.1. Test Compound Nomenclature.

Compound	
Common name	glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

3.2 Registered Application Scenarios

Glyphosate is registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Post-emergent applications are typically soil-directed for all but genetically modified crops where over-the-top applications are permitted. Harvest-aid (desiccant) applications are also registered for a number of cereal grain, legume vegetable, non-grass animal feed, and oilseed crops. The JGTF provided tables concerning the labeled application scenarios for the following products: EPA Reg. Nos.: 100-1182, 228-713, 524-343, 524-475, 524-537, 524-549, 524-579, 4787-23, and 62719-556. The information provided in the tables are an adequate representation of these labels with adequate residue data available to support the specified food/feed application scenarios. Glyphosate is also currently registered for application to turf (including golf courses and residential lawns) and for aquatic application

HED notes that there are additional registered products and requests that the registrants verify the following concerning the application scenarios specified for these products: (1) for each specific application scenario, the application rates are equal to or less than those specified in the above products and the RTI/PHI (retreatment interval/preharvest interval) are equal to or greater than those specified in the above products and (2) all food/feed crop labels indicate that treated fields may be rotated to a labeled crop at any time and may be rotated to a non-labeled crop 30 days after application.

3.3 Anticipated Exposure Pathways

Based on the registered agricultural and residential uses, dietary (food and water) and incidental oral (turf and aquatic application scenarios) exposures are possible and were assessed. Dermal and inhalation exposures are also anticipated but were not assessed due to the lack of toxicity via these routes (see Section 4.0). Humans may be exposed to glyphosate in food and drinking water, since glyphosate may be applied directly to growing crops and application may result in glyphosate reaching surface and ground water sources of drinking water. There are residential uses of glyphosate; and non-occupational exposure to glyphosate via spray drift is possible. There is the potential for dermal and inhalation exposures from the residential application of registered glyphosate products by adults. In addition, there is the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from contact with previously treated turf. Occupational exposures are expected from the application (dermal and inhalation) of glyphosate and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all of the proposed uses of glyphosate. Note that quantitative exposure assessments are conducted only if adverse effects are observed for the duration and route of exposure.

3.4 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant (see Attachment F). Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

The Agency strives to use high-quality studies when evaluating the hazard of pesticide chemicals and considers a broad set of data during this process. A wide range of potential adverse effects are assessed using acute, subchronic, chronic, and route-specific studies predominately from studies with laboratory animals in addition to epidemiologic and human incident data. All studies are thoroughly reviewed to ensure appropriate conduct and methodologies are utilized, and that sufficient data and details are provided.

For all pesticides, there are toxicology data requirements that must be submitted to the Agency for registration. These studies, defined under the 40 CFR Part 158 Toxicology Data Requirements, provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and lifestages. They typically follow the Organization for Economic Co-operation and Development (OECD) accepted protocols and guidelines, which ease comparisons across studies and chemicals. Data may also be available to elucidate a chemical's hazard from the open scientific literature, structurally related chemicals, physiologically-based pharmacokinetic (PBPK) or biological dose-response models, biomonitoring, or other exposure studies/analyses.

In 2012, OPP published a guidance document to provide guidance procedures for considering and using open literature toxicity studies to support human health risk assessment[1]. This guidance assists OPP scientists in their judgement of the scientific quality of open literature publications. More specifically, the document discusses how to screen open literature studies for journal articles/publications that are relevant to risk assessment, how to review potentially useful journal articles/publications and categorize them as to their usefulness in risk assessment, and how the studies may be used in the risk assessment.

In recent years, the National Academy of Sciences National Research Council (NRC) has encouraged the Agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making[2]. The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies"[3]. Consistent with NRC's recommendations, EPA's Office of Chemical Safety and Pollution Prevention is currently developing policies and procedures in order to employ fit-for-purpose systematic reviews.

The hazard characterization, evaluation of potential endpoints, selection of PODs, and the SFs for glyphosate reflect a weight-of-evidence evaluation across multiple lines of evidence. Consistent with Agency policy, this evaluation focuses on studies performed with the active ingredient glyphosate and not studies performed with pesticide formulations containing glyphosate. Many studies examining pesticide formulations containing glyphosate were evaluated in the literature review memo; however, none of the existing studies are sufficiently robust for deriving PODs for risk assessment.

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[1] U.S. EPA (2012). *Guidance for considering and using open literature toxicity studies to support human health risk assessment.* http://www.epa.gov/pesticides/science/lit-studies.pdf

[2] NRC 2011. "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde"; NRC 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process"

[3] NRC (2014). Review of EPA's Integrated Risk Information System (IRIS) process. Washington, DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=18764

4.1 Toxicology Studies Available for Analysis

The hazard database for glyphosate is complete. Since the 2012 risk assessment (D398547, T. Bloem *et al.*, 14-Nov-2012), immunotoxicity and neurotoxicity (acute and subchronic) studies have been submitted and reviewed, and are included in this hazard characterization. The current human health risk assessment also includes the re-evaluation of the carcinogenic potential of glyphosate. Attachment A includes a summary of the glyphosate toxicological database, and includes the following studies:

(1) Acute toxicity following oral, dermal and inhalation exposure; eye and dermal irritation and dermal sensitization;
(2) Acute and subchronic neurotoxicity in rats;
(3) Subchronic oral toxicity in rats, mice, and dogs;
(4) Subchronic dermal and inhalation toxicity in rats;
(5) Chronic toxicity in rats and dogs;
(6) Carcinogenicity in mice and rats;
(7) Developmental toxicity in rats and rabbits;
(8) Reproductive and postnatal toxicity in rats;
(9) Metabolism studies in rats;
(10) Immunotoxicity; and
(11) Mutagenicity/genotoxicity studies in *vivo* and *in vitro*.

A number of literature studies were either found via a systematic review of the open scientific literature or were submitted to the Agency. These studies have been considered as part of Registration Review (TXR #0056885). In conjunction with Health Canada's PMRA, a literature search was performed in late 2011 and early 2012. A total of 67 studies (obtained from 62 individual references) were reviewed for potential use in human health risk assessment. None of these studies had an impact on the hazard characterization or PODs selected for the Registration Review draft human health risk assessment for glyphosate. The majority of the literature studies were found to be unacceptable for a variety of reasons. For example, some studies did not meet the minimum criteria to be considered eligible (e.g., the study was not found to be the primary source of the data, was not publicly available, or not presented as a full article). Of the studies that met the minimum criteria, the most common limitations/deficiencies were related to the nature of the test substance(s) used for exposure (e.g., using commercial formulations, lack of test material validation). Most studies used commercial formulations or dilutions; however, direct measurements of the active ingredient were not conducted in order to determine actual dose concentrations and/or identification information was not provided for the formulation used (e.g., EPA registration number). As a result, potential effects could not be attributed to defined exposure concentrations. A limited number of studies were deemed acceptable and appropriate for consideration in risk assessment; however, any observed effects were observed at doses higher than the selected PODs.

As part of Registration Review, the Agency has reviewed and updated the experimental toxicology literature search since the joint search with PMRA, using the concepts consistent with systematic review, such as detailed tracking of search terms and which literature have been included or excluded. The literature review was conducted in PubMed for the time period January 2012 to October 2015 and yielded 392 articles. This list was then cross-referenced with other studies submitted during that time to the Agency by non-profit groups or members of the

public and another seven studies were added for review bringing the total number of articles to 399. Since the goal of the literature search was to identify relevant and appropriate open literature studies that had the potential to impact human health risk assessment, most of the studies were not considered to be within the scope of the search due to the subject of the research (i.e., ecological and fate studies, crop composition studies, pest management studies, method generating, hypothesis generating, exposure and monitoring) or not relevant in general. Additionally, several articles were not appropriate due to the type of article (i.e., review, commentary, editorial, article retraction, news article, abstract only, not available in English). Similar to the search conducted with PMRA, many of the studies concerning human health used commercial formulations; however, direct measurements of the active ingredient were not conducted in order to determine actual dose concentrations and/or identification information was not provided for the formulation used. As a result, potential effects could not be attributed to defined glyphosate exposure concentrations. None of the studies from this more recent review were found to have an impact on the hazard characterization or draft human health risk assessment for glyphosate.

Additionally, a systematic review of the open literature was performed in 2016 to identify relevant and appropriate open literature studies that could inform the human carcinogenic potential of glyphosate. Details and results of this systematic review can be found in the Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential (D444689; 12-DEC-2017; TXR#0057688)

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

A comprehensive review of the available data on the absorption, distribution, metabolism and excretion (ADME) of glyphosate was presented in the issue paper for the FIFRA Scientific Advisory Panel (SAP) in December, 2016[4]. In the issue paper, EPA reviewed 12 excretion, metabolism and tissue distribution studies with parent glyphosate, two metabolite disposition studies characterizing the disposition of AMPA and N-Nitroso-N-(phosphonomethyl)glycine (NPMG); and one metabolite disposition study with *N*-acetyl-glyphosate. The review also included a disposition study performed by NTP and two literature studies; a toxicokinetic study performed by Anadon *et al.* (2009), and a tissue distribution and metabolite quantification study performed by Brewster *et al.* (1991). An overall summary of these data are presented below.

Oral exposure is considered the primary route of concern for glyphosate. The maximum absorption from the GI tract for glyphosate was estimated to be approximately 30%-40% based upon radiolabel detected in the urine. In general, the amounts of glyphosate detected in tissues were negligible indicating low tissue retention following dosing. Parent glyphosate is the principal form excreted in urine and feces. The primary route of excretion following oral administration of glyphosate is the feces, as verified by the intravenous dosing and bile cannulation experiments. Within the dose ranges tested, elimination was essentially complete by 24 hours indicating that glyphosate does not bioaccumulate.

4- *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs, 2016.* https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

Multiple studies examined the pharmacokinetics of a single dose of radiolabeled glyphosate ranging from 5.6 – 400 mg/kg. Across these studies, time to reach peak plasma concentrations (T_{max}) appeared to increase with increasing dose; however, the reported range of T_{max} (1-5.5 hours) suggests only a slight shift in absorption kinetics occurs despite large increases in dose. In the one study that tested two doses[5], data graphically show that peak blood levels were only roughly 3-fold with a 10-fold increase between the two doses. Reported area under the curve (AUC) values indicated conflicting results regarding whether linear or non-linear absorption kinetics was occurring at higher doses.

4.2.1 Dermal Absorption

A dermal absorption study is not available in the toxicity database. However, a dermal absorption factor is not needed since no dermal hazard was identified and thus quantification of dermal risk is not required (see Section 4.5.1).

4.3 Toxicological Effects

Glyphosate exhibits low toxicity across species, durations, life stages and routes of exposure. In most of the studies in its hazard database, effects are seen at doses at or above the limit dose (>1000 mg/kg/day). A total 14 acceptable chronic toxicity/carcinogenicity studies (6 mouse and 8 rat) were available for review. Among the effects observed were decreases in body weights and minor indicators of toxicity to the eyes, liver, and kidney. There were no effects observed in route-specific dermal and inhalation studies. There is no evidence that glyphosate is neurotoxic or immunotoxic.

Glyphosate showed no evidence of increased quantitative or qualitative susceptibility following *in utero* exposure to rats or rabbits. In rats, maternal and developmental toxicity was seen at or above the limit dose. In rabbits, maternal toxicity manifested primarily as clinical signs (diarrhea, few/soft feces) and developmental toxicity (decreased fetal weight) was seen only at high doses. In a three-generation reproductive toxicity study conducted in 1981, prior to the establishment of the Part 158 Test Guidelines, there was an increased incidence of renal tubule dilation at doses which did not cause parental toxicity in the F_3 generation. This finding was judged to be spurious and unrelated to treatment since a more extensive evaluation in the two subsequent reproduction studies conducted at much higher doses in accordance with the Part 158 Test Guidelines did not replicate these findings. In a second reproduction toxicity study, offspring toxicity (decreased body-weight gain during lactation without a corresponding decrease in absolute body weight) was seen at the same dose that caused parental toxicity. In the third reproduction toxicity study conducted in accordance with the revised 1998 test protocol, offspring effects were observed above the limit dose in the absence of parental toxicity and consisted of delayed age (almost 3 days) and increased weight at attainment of PPS.

Glyphosate is categorized as having low acute toxicity following oral, dermal, and inhalation exposure, since all studies are in 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.

[5] NTP (1992). NTP technical report on the toxicity studies of Glyphosate (CAS No. 1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice. Toxic Rep Ser 16: 1-d3.

4.4 Safety Factor for Infants and Children (FQPA SF)

The Agency recommends that the FQPA SF be reduced to 1X. This recommendation is based on the considerations described in the subsequent sections.

4.4.1 Completeness of the Toxicology Database

The toxicology database for glyphosate is adequate for characterizing toxicity and quantification of risk for food and non-food uses. The following acceptable studies are available for evaluation: developmental toxicity studies in rats and rabbits, three multi-generation reproductive toxicity studies in rats, acute and subchronic neurotoxicity studies in rats; and chronic toxicity/carcinogenicity studies in mice and rats.

4.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity following acute and repeated exposures in the neurotoxicity battery or in the other toxicity studies.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The database contained two pre-natal developmental toxicity studies in rats and rabbits and three reproductive toxicity studies (two studies performed for two generations, 1 study performed for three generations). There is no evidence of increased susceptibility (quantitative or qualitative) following *in utero* exposures to rats and rabbits. In rats, no maternal or developmental toxicity was seen at any dose including the limit dose. In rabbits, developmental toxicity was seen at doses higher than the doses that caused maternal toxicity. In the three-generation study conducted in 1981 prior to the institution of the current Test Guidelines and Good Laboratory Practices, focal tubular dilation of the kidneys was observed in the offspring. This finding was judged to be spurious and unrelated to treatment since more extensive evaluations in subsequent reproduction studies conducted at much higher doses did not replicate the offspring effects. Of the two-generation reproduction studies, there was no evidence of increased susceptibility in the offspring in one study. In the other study conducted in accordance with the revised 1998 Test Guidelines, evidence of increased susceptibility in the offspring manifested as delayed age and increased weight at attainment in the absence of parental toxicity; however, concern is low for the offspring effects since the effects were observed above the limit dose (1000 mg/kg/day), a clear offspring NOAEL was established for the observed effects, there was no evidence of reproductive toxicity in the adults, and the PODs used for overall risk assessment would address this concern.

4.4.4 Residual Uncertainty in the Exposure Database

The dietary exposure analysis is conservative as it assumed tolerance level residues and 100% crop treated. The residential exposure analysis is also considered conservative as it is based on the 2012 Residential SOPs.

4.5 Toxicity Endpoint and Point of Departure Selections

A summary of the toxicological doses and endpoints for glyphosate used in human health risk assessment are summarized in table 4.5.4.

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint (All Populations): An acute reference dose (aRfD) was not established, based on the absence of an appropriate toxicological endpoint attributable to a single exposure (dose), including fetal toxicity in developmental toxicity studies.

Chronic Dietary Endpoint: The toxicology database contains long-term toxicity studies in mice, rats and dogs. However, these studies demonstrate that glyphosate is of very low toxicity following repeated oral exposure to experimental animals. In dogs, there was no evidence of toxicity at the highest dose (500 mg/kg/day) tested. Among the 14 combined chronic toxicity/carcinogenicity studies (6 mice and 9 rats), treatment-related effects were seen only at or near the limit dose in rats, and in mice at doses that exceeded the limit dose by over 4-fold. Rabbits were seen to be the most sensitive species. Consequently, the pre-natal developmental toxicity study in rabbits (MRID 44320616) was selected as the critical study for chronic dietary risk assessment. The POD is the maternal NOAEL of 100 mg/kg/day based on maternal toxicity (diarrhea, few and/or no feces) observed at the lowest-observed adverse-effect level (LOAEL) of 175 mg/kg/day and the highest dose tested (300 mg/kg/day). Similar clinical findings (diarrhea, soft and/or liquid feces, no feces) were also seen at the same dose (175 mg/kg/day) and at a higher dose (350 mg/kg/day) in another study in rabbits (MRID 00046362). Although this endpoint is not typically considered to be an adverse effect per se, it was seen in a dose-dependent manner in two studies, and is protective all of the other effects and durations in the database.

A chronic population adjusted dose (cPAD) of 1.0 mg/kg/day was derived from a maternal NOAEL of 100 mg/kg/day and the application of a 100-fold factor that included a 10X UF for inter-species extrapolations, 10X UF for intra-species variations, and a 1X FQPA SF. Since the endpoint of concern is based on maternal toxicity, it is appropriate to assess chronic dietary risk to all population subgroups. Furthermore, the cPAD will be protective of all the effects seen in the long-term studies in mice and rats. An additional SF for the use of short term study for long term risk assessment was not applied since the weight-of-evidence shows toxicity occurred at much higher doses in the other species and thus would provide adequate protection for long-term risk assessment.

Incidental Oral Short- and Intermediate-Term: The developmental toxicity study in rabbits was also chosen for the short- and intermediate-term incidental oral endpoint. The POD (i.e., maternal NOAEL) was 100 mg/kg/day based upon clinical signs of toxicity (diarrhea, few and/or no feces) at the LOAEL of 175 mg/kg/day. The LOC is 100 based upon a 100-fold factor that included a 10X UF for inter-species extrapolations, 10X UF for intra-species variations, and a 1X FQPA SF. The POD is appropriate for the population (i.e., infants and children) and duration of concern. It is also protective of the offspring effects observed above the limit dose in the multi-generation reproduction studies.

Short- and Intermediate-Term Dermal: A POD for short- and intermediate-term dermal exposure risk assessment was not selected since no dermal or systemic toxicity was seen at the limit dose (1000 mg/kg/day) following repeated dermal application to rabbits for 21-days. Although there is an increased postnatal quantitative susceptibility in one of the two-generation reproductive studies, the effects are observed above the limit dose through the oral route, and are of low concern for dermal risk assessment. Consequently, quantification of dermal risk is not required.

Short- and Intermediate-Term Inhalation: A POD for short- and intermediate-term inhalation exposure risk assessment was not selected since there were no portal of entry effects or systemic toxicity seen following inhalation exposure to rats up to the highest concentration tested (0.36 mg/L). Although there is an increased postnatal quantitative susceptibility in one of the two-generation reproductive studies, the effects are observed above the limit dose through the oral route, and are of low concern for inhalation risk assessment. Therefore, quantification of inhalation risk is not required.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Since PODs were not selected for assessing risks via the dermal and inhalation routes of exposure, combined risks from other routes are not required.

4.5.3 Cancer Classification and Risk Assessment Recommendation

As part of Registration Review, the Agency reevaluated the human carcinogenic potential of glyphosate. The Agency collected and analyzed a substantial amount of data informing the carcinogenic potential of glyphosate and utilized the "Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment."[6] The framework provides the foundation for evaluating multiple lines of scientific evidence and includes two key components: problem formulation and use of the mode-of-action/adverse-outcome-pathway (MOA/AOP) frameworks. A comprehensive analysis of data on glyphosate from submitted guideline studies and the open literature was performed. This includes epidemiological, animal carcinogenicity, genotoxicity, metabolism, and mechanistic studies. Guideline studies were collected for consideration from the toxicological databases for glyphosate and glyphosate salts. A fit-for-purpose systematic review was executed to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate. Furthermore, the list of studies obtained from the toxicological databases and systematic review was cross-referenced with recent internal reviews, review articles from the open literature, international agency evaluations, and a list of studies provided by registrants.

Available data from epidemiological, animal carcinogenicity, and genotoxicity studies were reviewed and evaluated for study quality and results to inform the human carcinogenic potential of glyphosate according to the 2005 Guidelines for Carcinogen Risk Assessment. Additionally, multiple lines of evidence were integrated in a weight-of-evidence analysis using the modified Bradford Hill Criteria considering concepts, such as strength, consistency, dose response, temporal concordance, and biological plausibility. The totality of the data has been used by the Agency to inform cancer classification descriptors according to the 2005 Guidelines for Carcinogen Risk Assessment.

In December 2016, the Agency convened the FIFRA SAP to review this evaluation and the evaluation was subsequently updated to address their comments[7]. Based on a weight-of-evidence evaluation, the Agency has concluded that glyphosate is classified as "not likely to be carcinogenic to humans." (D444689; 12-DEC-2017; TXR# 0057688 and G. Akerman, 12-DEC-2017; D444688; TXR#0057689)

6 https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf
7 https://www.epa.gov/sap/fifra-scientific-advisory-panel-meetings

4.5.4 Summary of PODs and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4. Summary of Toxicological Doses and Endpoints for Glyphosate for Use in Human Health Risk Assessments[1].

Exposure/ Scenario	POD	Uncertainty/ FQPA SF	RfD, PAD, LOC	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	An endpoint of concern (effect) attributable to a single dose was not identified in the database. Quantification of acute dietary risk to general population including infants and children is not required.			
Chronic Dietary (All Populations)	NOAEL = 100 mg/kg/day	UF_A = 10x UF_H =10x FQPA SF = 1x	cPAD = cRfD = 1.00 mg/kg/day	Developmental Toxicity Study – Rabbit (MRID 44320616): Maternal LOAEL = 175 mg/kg/day based on dose-dependent clinical signs (diarrhea, few and/or no feces). These findings were also seen in another study in rabbits at a similar same dose (MRID 00046362).
Short- (1-30 days) and Intermediate-(1-6 months) Term Incidental Oral	NOAEL = 100 mg/kg/day	UF_A = 10x UF_H =10x FQPA SF = 1x	LOC (residential) = MOE < 100	Developmental Toxicity Study – Rabbit (MRID 44320616): Maternal LOAEL = 175 mg/kg/day based on dose-dependent clinical signs (diarrhea, few and/or no feces). These findings were also seen in another study in rabbits at a similar same dose (MRID 00046362).
Short- (1-30 days), Intermediate (1-6 months) Term Dermal	A dermal endpoint was not selected; therefore, quantification of dermal risks is not required.			
Short- (1-30 days), Intermediate (1-6 months) Term Inhalation	An inhalation endpoint was not selected, therefore, quantification of inhalation risks is not required.			
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be carcinogenic to humans."			

[1] UF = uncertainty factor, FQPA SF = FQPA Safety Factor, NOAEL = no-observed adverse-effect level, LOAEL = lowest-observed adverse-effect level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, HDT = highest dose tested, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies).

4.6 Endocrine Disruption

As required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints that may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its Registration Review for glyphosate, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), glyphosate is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required

determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[8] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Glyphosate is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2009-0361). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[9]

5.0 Dietary Exposure and Risk Assessment

The registrants have adequately addressed the residue chemistry deficiencies identified in the scoping document (D361315, T. Bloem, 14-Jan-2010).

5.1 Summary of Plant and Livestock Metabolism Studies

Primary Crops: Metabolism studies conducted with non-transgenic crops have been previously submitted and reviewed. Studies in corn, cotton, soybeans, and wheat indicate that the uptake of glyphosate from soil is limited, but the residues which are taken up are readily translocated. Foliarly applied glyphosate is readily absorbed and translocated throughout apples, coffee, dwarf citrus, grapes and pears. Metabolism occurs via *N*-methylation and ultimately yields *N*-methylated glycines and phosphonic acids. Based on these data, HED concluded that the residue of concern in non-transgenic plants is glyphosate (D. Duffy, 3-Jun-1974; C. Trichilo, Reregistration Standard, 15-Jul-1985; D179870, R. Perfetti, 13-Oct-1992; D183202 (RED), R. Perfetti, 27-Oct-1992; R. Perfetti, 17-Mar-1994). Metabolism studies have also been submitted on glyphosate-tolerant canola (RT73; D242628, T. Bloem, 30-Nov-1998) and glyphosate-tolerant field corn (Roundup Ready® field corn; D217539, G. Kramer, 14-Mar-1996). The glyphosate-tolerant canola and field corn varieties were genetically modified to express the EPSPS gene derived from *Agrobacterium sp.* (strain CP4) which codes for an EPSPS protein that is not inhibited by glyphosate. The glyphosate-tolerant canola and corn were also genetically engineered to express the oxidoreductase gene which codes for a protein that converts glyphosate to the non-herbicidal AMPA. Metabolism

8 See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
9 http://www.epa.gov/endo/

in these varieties of transgenic canola and corn was essentially the same as the non-transgenic plants. Therefore, it was concluded that the terminal residue to be regulated, in non-transgenic plants and transgenic corn and canola modified to express the *Agrobacterium sp.* EPSPS and oxidoreductase genes, is glyphosate.

Subsequent to these decisions, HED approved DuPont requests concerning application of glyphosate to Optimum™ GAT™ soybean, Optimum™ GAT™ field corn, and Optimum® GLY Canola. These soybean, field corn, canola varieties were genetically engineered to express the *gat*4601 or *gat*4621 genes (derived from *Bacillus licheniformis*; soil bacterium) which confer tolerance to glyphosate via conversion of parent to the non-herbicidal *N*-acetyl-glyphosate. The Optimum™ GAT™ field corn and soybean varieties were also engineered to express the *zm-hra* gene (modified version of the acetolactate synthase (ALS) gene) which encodes for an ALS protein which is not sensitive to the ALS-inhibiting herbicides. As a result of the introduction of these seed lines, HED concluded that the residues of concern in soybean, field corn, and canola for tolerance expression and risk assessment should change from glyphosate to the combined residues of glyphosate and *N*-acetyl-glyphosate (expressed in glyphosate equivalents; D346713, T. Bloem, 12-Mar-2008; D357880, T. Bloem, 29-Oct-2008; D361315, T. Bloem, 14-Jan-2010; D394964, T. Bloem, 15-Nov-2011).

Livestock: The qualitative nature of the residue in livestock following dosing with glyphosate and AMPA is adequately understood. Studies with lactating goats and laying hens fed a mixture of glyphosate and AMPA indicate that the primary route of elimination was by excretion (urine and feces). The HED Metabolism Assessment Review Committee (MARC) determined that the terminal residue to be regulated in livestock is glyphosate (D179870, R. Perfetti, 13-Oct-1992; D183202 (RED), R. Perfetti, 27-Oct-1992; R. Perfetti, 17-Mar-1994).

Since the Optimum™ GAT™ soybean and field corn metabolism studies resulted in significant residues of *N*-acetyl-glyphosate, DuPont submitted summaries of *in vitro* (rumen fluid, fertile hen egg, and rat liver S9 supernatant) and *in vivo* (rat metabolism study) studies conducted with the *N*-acetyl-glyphosate metabolite and submitted goat and hen metabolism studies conducted with the *N*-acetyl-glyphosate metabolite. Based on these data and the glyphosate metabolism studies, HED concluded that the residues of concern in livestock following consumption of glyphosate and *N*-acetyl-glyphosate, for tolerance expression and risk assessment purposes, are glyphosate and *N*-acetyl-glyphosate (D346713, T. Bloem, 12-Mar-2008; D361315, T. Bloem, 14-Jan-2010).

Rotational Crops: A confined rotational crop study has been previously submitted/reviewed which employed an application rate of 3.7 lb ae/acre and carrot, lettuce, and barley as rotational crops (plantback intervals (PBIs) of 30, 119-125, and 364 days; MRIDs 415432-01 and -02, A. Abramovitch, 14-Oct-1992). Glyphosate residues were <0.01 ppm in/on all rotational crops except for barley grain from the 125-day PBI plot which had a glyphosate residue of 0.018 ppm. Based on these data, HED concluded that residues in rotational crops will be insignificant provided the labels specify a 30-day PBI for all nonlabeled crops (D200041, G. Kramer, 12-May-1994; field rotational crop study has not been submitted and is not required).

Environmental Fate: It is assumed that the glyphosate salts dissociate rapidly to form glyphosate acid and the counter ion. Because glyphosate acid will be a zwitterion (presence of both negative (anionic) and positive (cationic) electrostatic charges) in the environment, it is expected to speciate into dissociated species of glyphosate acid in soil, sediment, and aquatic environments. The

environmental fate data for glyphosate, with the exception of a photodegradation study (MRID 44320643), did not address the impact of environmental fate processes on different species of glyphosate acid.

The major route of transformation of glyphosate identified in laboratory studies is microbial degradation. In soils incubated under aerobic conditions, the half-life of glyphosate ranges from 1.8 to 109 days and in aerobic water-sediment systems is 14 - 518 days. However, anaerobic conditions limit the metabolism of glyphosate (half-life 199 - 208 days in anaerobic water-sediment systems). In laboratory studies, glyphosate was not observed to break down by abiotic processes, such as hydrolysis, direct photolysis on soil, or photolysis in water at pH 7. In the field, soil dissipation half-lives for glyphosate were measured to be 1.4 - 142 days. Although the variability in glyphosate dissipation rates cannot be statistically correlated to any specific test site properties, dissipation half-lives tend to be higher at test sites in the central to northern United States. Along with significant mineralization to carbon dioxide, the major degradate of glyphosate is AMPA.

The available field and laboratory data indicate that glyphosate adsorbs strongly to soil. Based on the low vapor pressure of glyphosate, volatilization from soils will not be an important dissipation mechanism. HED concluded that glyphosate is the only residue of concern in drinking water.

5.2 Residues of Concern Summary and Rationale

As indicated in Section 4.2, the only identified metabolite from the rat metabolism study was AMPA which was found in the excreta. Excluding the DuPont glyphosate-tolerant plant metabolism studies, the plant and livestock metabolism studies resulted in a similar profile with glyphosate and AMPA being the main residues. In the DuPont glyphosate-tolerant plant metabolism studies, *N*-acetyl-glyphosate was also a major residue. *N*-acetyl-glyphosate is not anticipated to be more toxic than glyphosate based on the available toxicity data, similar structure to glyphosate, and the lack of lack of structural alerts for carcinogenicity, mutagenicity and endocrine effects (D345923, P. Shah *et al.*, 18-Mar-2008).

In 1992, the HED Metabolism Committee determined that, based on toxicological considerations, AMPA need not be regulated, and in 1994, it was determined that, based on toxicological considerations, AMPA need not be regulated regardless of levels observed in foods or feeds. *N*-acetyl-AMPA was detected as one of the metabolites formed in certain transgenic crops and was excluded as a residue of concern based on residue and toxicity considerations (D345923, P. Shah *et al.*, 18-Mar-2008). The decision that AMPA and *N*-acetyl-AMPA need not be regulated, regardless of levels observed in foods or feeds, was revisited for the glyphosate registration review risk assessment. HED believes the decision to not regulate AMPA is still appropriate based on the following toxicological considerations: (1) the parent active ingredient glyphosate has a very low level of toxicity based on HED's database of guideline studies; (2) glyphosate toxicity studies are being used in endpoint selection; (3) the effects in the available subchronic study for AMPA (body weight loss and histopathologic lesions of the urinary bladder) occur at a dose greater than the limit dose (1,200 mg/kg/day) which is four fold higher than the point of departure being used in risk assessment; and (4) the points of departure selected are protective for the observed toxicity due to AMPA.

A summary of the residues of concern in primary crops, livestock, rotational crops, and drinking water for the tolerance expression and dietary risk assessments is presented in Table 5.2.

Table 5.2. Residues of Concern for Tolerance Expression and Risk Assessment.		
Matrix	Residues Included in Risk Assessmen	Residues Included in Tolerance Expressior
primary crops (excluding soybean and field corn)	glyphosate	glyphosate
soybean and field corn	glyphosate and *N*-acetyl-glyphosate	glyphosate and *N*-acetyl-glyphosate
livestock	glyphosate and *N*-acetyl-glyphosate	glyphosate and *N*-acetyl-glyphosate
rotational crops	glyphosate	glyphosate
drinking water	glyphosate	not applicable

5.3 Food Residue Profile

For most crops, tolerances are at or near the LOQ and reflect the fact that only soil-directed applications are permitted. Significantly higher tolerance are established for those crop where harvest-aid (desiccant) applications are registered and for the tolerant crops where over-the-top applications are permitted.

Provided all labels conform to the application scenarios specified in the JGTF summary (see Section 3.2), the residue chemistry database is sufficient to support the current registrations; no additional residue chemistry data are required. HED evaluated the glyphosate residue chemistry database to determine if the established tolerances conform to the current practices and to determine if the crop group/subgroup tolerances could be updated to the current crop group/subgroup definitions. Based on this analysis, HED is recommending for establishment of the tolerances listed in Attachment C Table C.1. A subgroup 24D tolerance was not recommended as glyphosate is not registered for application to dragon fruit (representative crop). It is noted that for the remaining recommended crop groups/subgroup tolerances, the application scenarios within a crop group/subgroup were not consistent in every instance. Despite this, HED is recommending for the crop group/subgroup tolerances as the differences were minor and unlikely to lead to a significant difference in residues. With the establishment of the tolerances listed in Attachment C Table C.1, the following tolerances should be deleted: acerola; aloe vera; ambarella; asparagus; atemoya; avocado; bamboo, shoots; banana; biriba; breadfruit; cactus, fruit; cactus, pads; canistel; cherimoya; custard apple; date, dried fruit; durian; feijoa; fig; fruit, stone, group 12; guava; ilama; imbe; imbu; jaboticaba; jackfruit; longan; lychee; mamey apple; mango; mangosteen; marmaladebox; noni; nut, tree, group 14; olive; palm heart; papaya; papaya, mountain; passionfruit; pawpaw; persimmon; pineapple; pistachio; pomegranate; pulasan; rambutan; rose apple; sapodilla; sapote, black; sapote, mamey; sapote, white; soursop; Spanish lime; star apple; starfruit; sugar apple; Surinam cherry; tamarind; vegetable, leafy, brassica, group 5; vegetable, leafy, except brassica, group 4; watercress, upland; and wax jambu.

In response to concern from segments of the general public related to the presence of glyphosate in human milk, the 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 (ACB Project #B14-46, L. Podhorniak, 13-May-2015). A total of 39 samples from 39 mothers were analyzed using a fully validated liquid chromatography with tandem mass spectroscopy (LC-MS/MS) method which has a high level of specificity for the target analytes. Glyphosate, *N*-acetyl-glyphosate, and AMPA were not detected in the samples (glyphosate LOQ/LOD = 10 ppb/3.3 ppb; metabolite LOQ/LOD = 30 ppb/10 ppb). Storage stability data are available validating the storage interval (ACB Project #B14-46, L. Podhorniak, 26-Apr-2016).

5.4 Drinking Water Residue Profile

D440486, J. Hetrick, 15-Jun-2017

Table 5.4 is a summary of the worst-case EDWCs when considering all registered uses. Based on these estimates, the chronic dietary assessment assumed a concentration in water of 75 ppb. The monitoring data provided in Table 5.4 were derived from the United States Geological Survey (USGS) National Water-Quality Assessment Program (NAWQA). The groundwater monitoring data with high glyphosate concentrations provided in Table 5.4 are associated with subsurface drains and, therefore, they are not representative of groundwater sourced drinking water. Typically, tile drain fields form preferential flow pathways into tile drains, which allows for a less torturous flow pathway when compared to advection-dispersion flow, as assumed in the groundwater model.

Table 5.4. Drinking Water Concentrations.

Drinking Water Source	Crop Scenario/Model	1-in-10-year average daily (µg/L)	1-in-10-year annual average (µg/L)
Surface Water	direct application to surface water/Pesticide Water Calculator (ver. 1.52) and Variable Volume Water Model (ver. 1.02).	700	**75**
	monitoring[2]	35	2.8
Ground Water	Crop Scenario/Model	Peak (µg/L)	Post-Breakthrough Average (µg/L)
	turf - 40 lbs ae/acre/PRZM-GW (ver. 1.52)[1]	no breakthrough	
	monitoring[3]	285	20.6

[1] PRZM-GW = pesticide root zone mode- groundwater
[2] Monitoring sites with dissolved glyphosate data and watershed areas greater or equal to 0.04 km^2 are assumed to be capable of supporting a CWS. A watershed area of 0.04 km^2 represents a lower bound watershed area for a surface source drinking water.
[3] The indicated highest glyphosate concentration in groundwater is from a subsurface drain in Hamilton County, IA (USGS 423232093351801), which is not representative of a drinking water intake location.

5.5 Dietary Risk Assessment

D429229, T. Bloem, 30-Nov-2017

A chronic dietary risk assessment was conducted using DEEM-FCID (ver. 3.16) which incorporates consumption data from USDA NHANES/WWEIA (2003-2008). Acute and cancer dietary risk assessments were not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup and glyphosate is classified as not likely to be a human carcinogen, respectively. The chronic analysis is highly conservative in that it assumed tolerance-level residues, 100% crop treated, DEEM (ver. 7.81) default processing factors, and modeled drinking water estimates (direct application to water scenario). The resulting chronic risk estimates (food and water) were <100% of the cPAD and are therefore less than HED's level of concern (children 1-2 years old were the most highly exposed population subgroup at 23% the cPAD). Table 5.5 is a summary of the chronic dietary exposure estimates.

Table 5.5. Summary of Chronic Dietary Exposure and Risk.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD[1]
General U.S. Population	1.00	0.089771	9.0
All Infants (< 1 year old)		0.138338	14
Children 1-2 years old		**0.228379**	**23**
Children 3-5 years old		0.212036	21
Children 6-12 years old		0.147749	15
Youth 13-19 years old		0.088362	8.8
Adults 20-49 years old		0.074650	7.5
Adults 50-99 years old		0.061258	6.1
Females 13-49 years old		0.069318	6.9

[1] The bolded %cPAD represents the population with highest risk.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

D398862, L. Venkateshwara, 30-Oct-2012

Residential exposure to glyphosate may occur as a result of the currently registered turf (including golf courses and residential lawns) and aquatic application scenarios. These uses were previously assessed in 2012 (Memo, L. Venkateshwara, D398862, 30-Oct-2012), and that assessment reflects HED's 2012 Residential SOPs, policy changes for body-weight assumptions, and updates to HED's inputs for aquatic/swimmer assessments. The exposure and risk estimates from the previous assessment are summarized here. It should be noted, however, that the MOEs have been updated to reflect a revised POD, the aquatic use scenario has been updated to reflect a higher application rate identified in the JGTF use matrix, and the aquatic scenario inputs have been updated to reflect the draft Aquatic SOP (November, 2015).

6.1 Residential Handler Exposure

Based on the registered residential use patterns, there is a potential for short-term dermal and inhalation exposures to homeowners who mix and apply products containing glyphosate (residential handlers). However, since short- and intermediate-term dermal and inhalation PODs were not selected due to the lack of toxicity via these routes, a quantitative exposure risk assessment was not completed.

6.2 Post-Application Exposure

Post-application dermal and inhalation assessments were not quantitatively assessed since short- and intermediate-term dermal or inhalation PODs were not selected. However, based on the registered use patterns, children may have short-term post-application incidental oral exposures from hand-to-mouth behavior on treated lawns and swimmers (adults and children) may have short-term post-application incidental oral exposures from the aquatic use. It is noted that the short-term assessment is protective of intermediate-term exposure as the incidental oral PODs for these durations are identical.

Table 6.2.1 presents the post-application incidental oral MOE values calculated for children 1 to <2 years old after applications of glyphosate to turf. Table 6.2.2 presents the post-application incidental oral ingestion MOE values calculated for adults and children 3 to <6 years old after aquatic applications of glyphosate. The post-application MOEs do not exceed the LOC for any of the scenarios assessed (LOC for MOEs <100). It is noted that the lifestages selected for risk assessment are considered protective for the exposures and risks for any other potentially exposed lifestages.

The incidental oral scenarios for the turf assessment (i.e., hand-to-mouth, object-to-mouth, and soil ingestion) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. Combining these scenarios would be overly-conservative because of the conservative nature of each individual assessment. Therefore, none of the incidental oral scenarios were combined.

ED_004926A_00022402-00022

Table 6.2.1. Post-application Incidental Oral Risk Estimates for Application of Glyphosate to Turf[1].

Lifestage	Post-application Exposure Scenario		Exposure (mg/kg/day)	Short-term MOEs[5]
Children 1 to <2 year old	Turf – sprays	Hand-to-Mouth[2]	0.1565	640
		Object-to-Mouth[3]	0.00481	21,000
		Incidental Soil Ingestion[4]	0.00034	290,000

[1] Based on the maximum labeled rate specified in the Roundup® Weed & Grass Super Concentrate, EPA Reg. No. 71995-25.
[2] Hand-to-Mouth = Hand residue loading (mg/cm^2)*fraction hand surface area mouthed/event (0.127/event)*typical surface area of one hand (150 cm^2)*exposure time (1.5 hrs/day)*number of replenishment intervals/hr (4 intervals/hr)*(1-(1-saliva extraction factor (0.5)^number of hand-to-mouth contact events per hour (13.9 events/hr); *Hand Residue Loading* = fraction of ae on hands compared to total surface residue from dermal TC study (0.06)*dermal exposure (mg))/typical surface area of one hand (150 cm^2).
[3] Object-to-Mouth = ((Object Residue (µg/cm^2)*CF1 (1.0E-3 mg/µg)*Object Surface Area Mouthed/Event (10 cm^2/event))*(Exposure Time (1.5 hrs/day)*#Replenishment Intervals/hr (4))*(1-((1-Extraction by Saliva (0.48))^(#Object-to-Mouth Events/hr (8.8 events/hr)/#Replenishment intervals/hr))))/Body Weight (11 kg).
[4] Soil Ingestion = (Soil Residue (7.0746975 µg/g) *Ingestion Rate (50 mg/kg/day) *CF(0.000001))/Body Weight (11 kg).
[5] MOE = NOAEL/Daily Dose (mg ae kg/day); Oral NOAEL = 100 mg/kg/day. LOC is for MOEs <100.

Table 6.2.2. Post-Application Swimmer Risk Estimates for Aquatic Application of Glyphosate.

Exposure Scenario	Application Rate (lb ae/acre)[1]	Maximum Concentration in water (mg/L)[2]	Exposure (mg/kg/day)[3]	Short-term MOE[4]
Ingestion of water, Adult	8	0.737	0.000046035	2,200,000
Ingestion of water, Children 3 to <6 years old			0.000484583	210,000

[1] Application rate from registered labels for aquatic weed control using glyphosate IPA salt (label = EPA Reg. No. 524-343 identified in the JGTF Use Matrix as the highest aquatic rate). Note this rate is higher than previously assessed in D398862.
[2] Maximum concentration in water (top 4 ft) = 8 lb ae/acre x 1A/43,560 ft^2 x 454,000 mg/lb x 4ft x ft^3/28.32 L = 0.737 mg/L.
[3] PDR, incidental oral exposure = concentration, C_w (mg/L) x ingestion rate, IgR (L/hr) x exposure time, ET (hrs/d) x 1/BW (adult = 80 kg; children (3 to <6 years old) = 19 kg).
[4] MOE = NOAEL/PDR; short-term incidental oral NOAEL = 100 mg/kg bw/d. LOC is for MOEs <100.

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3 reflects the residential risk estimates that are recommended for use in the aggregate assessment. The recommended residential exposure scenario for use in the adult aggregate assessment reflects short-term incidental oral exposure to treated aquatic areas (post-application exposure). The recommended residential exposure scenario for use in the child aggregate assessment reflects short-term incidental oral exposure to children 1 to <2 years old from treated turf (post-application exposure). As indicated above, the short-term assessment is protective of intermediate-term exposure (identical incidental oral POD for these durations) and the lifestages selected for aggregate risk assessment are considered protective for the exposures and risks for any other potentially exposed lifestage.

Table 6.3. Recommendations for the Residential Exposures for the Glyphosate Aggregate Assessment.

Lifestage	Exposure (mg/kg/day)[1]			Total Exposure (mg/kg/day)	MOE[2]
	Dermal	Inhalation	Oral		
short-term					
Adults	not applicable		0.000046035	0.000046035	2,200,000
Children 1 to <2 year old			0.1565	0.1565	640

[1] Post-application exposure represents high-end incidental oral exposure for the relevant exposure duration.
[2] Residential post-application MOE = Incidental oral NOAEL / Residential post-application total exposure; LOC for MOEs <100.

6.4 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-

0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for glyphosate.

6.5 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[10] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Several glyphosate products have existing labels for use on turf, thus it was considered whether the risk assessment for that use would be considered protective of any type of exposure that would be associated with spray drift. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. The currently registered maximum single agricultural application rate of glyphosate for several scenarios is at 8.0 lb ae/acre (grass pastures, forestry, and Christmas tree farms). The highest fraction of spray drift noted for any application method immediately adjacent to a treated field results in a deposition fraction of 0.26[11] of the application rate. A quantitative spray drift assessment for glyphosate is not required because the maximum application rate for the relevant uses multiplied by the 0.26x adjustment factor for drift (8.0 lb ae/acre x 0.26 = 2.08 lb ae/acre) is less than the assessed maximum direct spray residential turf application rate (10.5 lb ae/acre; D398862, L. Venkateshwara, 30-Oct-2012). As a result, the turf post-application assessment is protective for any potential exposures for any glyphosate products. The turf post-application MOEs have been previously assessed and are based on the revised SOPs for Residential Exposure Assessment (i.e., see above in Section 6.2).

10 This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.
11 Tier 1 output from the aerial application using fine to medium spray quality based on AgDrift® output files

7.0 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. Acute and cancer aggregate risk assessments were not conducted since an appropriate endpoint attributable to a single dose was not identified for the general U.S. population or any population subgroup and glyphosate is classified as not likely to be a human carcinogen, respectively. In addition, although an intermediate-term assessment was not conducted, the short-term assessment is protective of intermediate-term as the PODs for these durations are identical.

Short-Term Aggregate Risk Assessment: For children, short-term aggregate exposure includes chronic dietary (food and water) and incidental oral ingestion exposure resulting from the turf use (highest exposure of all possible scenarios). For adults, short-term aggregate exposure includes chronic dietary exposure (food and water) and incidental oral ingestion exposure resulting from the aquatic use (highest exposure of all possible scenarios). Table 7.0 is a summary of the short-term aggregate exposures and risk estimates. Since the aggregate MOEs are ≥260, short-term aggregate exposure to glyphosate does not exceed the LOC (LOC for MOEs <100). HED notes that the lifestages selected for short-term aggregate risk assessment and the resulting aggregate MOEs are protective for any other potentially exposed lifestage.

Table 7.0. Short-Term Aggregate Exposure.

Population	Exposure (mg/kg/day)			Aggregate MOE[2]
	Dietary[1]	Incidental Oral[1]	Combined	
Adults 20-49 years old	0.076405	0.000046035	0.076451	1,300
Children 1 to <2 year old	0.230916	0.1565	0.387416	260

[1] See Table 5.4 (dietary) and Table 6.3 (incidental oral); highest dietary exposure for children and adults was selected.
[2] Aggregate MOE = 100 mg/kg/day (short-term incidental oral NOAEL) ÷ combined exposure (mg/kg/day).

Chronic Aggregate Risk Assessment: Since there are no long-term exposures expected based on the use pattern, aggregate chronic risk assessment only takes into consideration dietary (food and water) exposure only. The chronic aggregate exposure and risk estimates do not exceed HED's LOC (≤23% cPAD; see Section 5.4).

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to glyphosate and any other substances. For the purposes of this assessment, therefore, EPA has not assumed that glyphosate has a common mechanism of toxicity with other substances. In 2016, EPA's OPP released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis*[12]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening

12 https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework

approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[13] and conducting cumulative risk assessments (CRA)[14]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for glyphosate suggests a candidate CMG may be established with other pesticides. If a CMG is established, then a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

9.0 Occupational Exposure/Risk Characterization

There is the potential for occupational handler and post-application dermal and inhalation exposure; however, due to the lack of toxicity via these routes, no dermal or inhalation PODs were selected for glyphosate. Therefore, a quantitative occupational exposure assessment was not conducted.

Restricted Entry Interval: Glyphosate is classified as Toxicity Category IV via the dermal route and Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Short- and intermediate-term post-application were not quantitatively assessed since short- and intermediate-term dermal endpoints were not selected. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to glyphosate.

REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of WPS Interim REIs for Certain Low Risk Pesticides]15. In PR Notice 95-3, there are a set of criteria listed for the active ingredient that must be met for chemicals to be eligible for a reduced REI. These criteria include:

- The active ingredient is in Toxicity Category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation. Acute oral toxicity data were used if no acute dermal data were available. If EPA lacked data on primary skin irritation, acute inhalation, or primary eye irritation of the active ingredient, then the Agency reviewed data on that end-point for similar active ingredients (analogs), and excluded such active ingredients from consideration for the reduced REI, if the analog is in Toxicity Category I or II for that endpoint.
- The active ingredient is not a dermal sensitizer (or in the case of biochemical and microbial active ingredients, no known reports of hypersensitivity exist).
- The active ingredient is not a cholinesterase inhibitor (N-methyl carbamate and organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.
- No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the active ingredient. If active ingredients did not have data available for these chronic health effects, then EPA considered data on appropriate chemical and biological analogs. Active ingredients that have been classified as carcinogenic in Category B (probable human carcinogen) or Category C with a potency factor, Q* (possible human carcinogen, for which quantification of potential risk is considered appropriate), or are scheduled for HED's Cancer Peer Review process, were omitted from consideration.

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13 Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999).
14 Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002).
15 Available: http://www.epa.gov/PR_Notices/pr95-3.html

●EPA does not possess incident information (illness or injury reports) that are "definitely" or "probably" related to post-application exposures to the active ingredient.

Upon review of the criteria for the active ingredient only, it appears that glyphosate is consistent with the criteria in PRN 95-3 that allow for a 4-hour REI. **Note**: *The PR Notice also includes similar criteria for the end-use product. These criteria have not been evaluated by HED.* Based solely on the active ingredient criteria, HED would recommend for reduction of the REI for glyphosate.

10.0 Incident and Epidemiological Analysis

D417808, S. Recore *et al.*, 6-Feb-2014

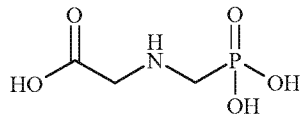
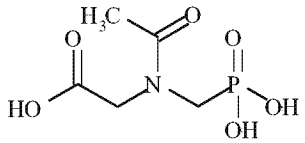
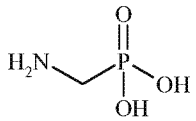
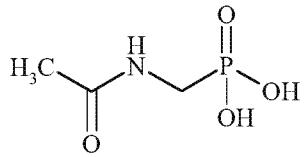
HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. Effects are generally mild/minor to moderate meaning the symptoms were minimally traumatic and resolved rapidly. The relatively high (absolute) number of reported glyphosate incidents across the reviewed databases is likely a result of glyphosate being among the most widely used pesticides by volume. It should be noted that most of the incidents reported are minor in severity. Pesticide Incidents from OPP Incident Data System (IDS; 2008 to 2012), California's Pesticide Incident Surveillance Program (PISP; 2005 to 2010), Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides (1998 to 2009), the Agency-sponsored National Pesticide Information Center (NPIC; 2007-2013), and American Association of Poison Control Centers (AAPCC; 2001 to 2012) data were reviewed. The incident data available from IDS and NPIC suggest that homeowner mixing/loading/applying (usually due to human errors and container leaks) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that application of glyphosate results in the most reported incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction. Based on the data in SENSOR, IDS, and NPIC, it appears that the children's exposures are due to postapplication exposure, accidental ingestion, and tampering with the product.

The medical-case literature reviewed indicates that most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self-limited. However, intentional ingestions caused moderate to severe symptoms and involved multiple organ systems.

While HED identified several dozen glyphosate environmental epidemiology studies, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes, and most studies were hypothesis-generating in nature. Given this and other limitations of these studies, there is insufficient evidence to conclude that glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in certain cancer and non-cancer outcomes.

Attachment A: Chemical Names and Structures.
Attachment B: Toxicity Profile Tables.
Attachment C: HED-Recommended Tolerances and International Residue Limits.
Attachment D: Physicochemical Properties.
Attachment E: References
Attachment F: Dietary Exposure Estimates Associated with Subsistence Fishing.

Attachment A: Chemical Names and Structures

Compound	Structure
Glyphosate *N*-(phosphonomethyl)glycine	
N-Acetyl-glyphosate *N*-acetyl-*N*-(phosphonomethyl)glycine	
AMPA (aminomethyl)phosphonic acid	
N-Acetyl-AMPA [(acetylamino)methyl]phosphonic acid	

Attachment B: Toxicity Profile Tables

B.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for uses of glyphosate are in Table B.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table B.1. Toxicological Data Requirements for Glyphosate.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	no[1]
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	no[2]
870.3200	21-Day Dermal	yes	yes
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	no
870.7800	Immunotoxicity	yes	yes

[1] The requirement for an acute inhalation LC_{50} study was waived.

[2] This is not considered a data gap because there is a chronic dog study in the database.

Table B.2. Acute Toxicity Profile.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	41400601	LD_{50} > 5,000 mg/kg	IV
870.1200	Acute dermal [rabbit]	41400602	LD_{50} > 5,000 mg/kg	IV
870.1300	Acute inhalation	None	The requirement for an acute inhalation LC_{50} study was waived	None
870.2400	Acute eye irritation [rabbit]	41400603	Corneal opacity or irritation clearing in 7 days or less	III
870.2500	Acute dermal irritation [rabbit]	41400604	Mild or slight irritant	IV
870.2600	Skin sensitization [guinea pig]	41642307	Not a sensitizer	None

Table B.3. Subchronic, Chronic, and Other Toxicity Profile.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day Oral Toxicity (Mice)	00036803 (1979) Acceptable/guideline 0, 5000, 10000, 50000 ppm (0, 944/ 1530, 1870/2740, 9710/ 14800 mg/kg/day [M/F])	NOAEL = 1870/2740 mg/kg/day [M/F]. LOAEL = 9710/14800 mg/kg/day [M/F] based on decreased body weight.
9870.3100	90-Day oral toxicity range finding (Rat)	40559401 (1987) Acceptable/guideline 0, 1000, 5000, or 20000 ppm (0, 63, 317, 1267 mg/kg/day)	NOAEL = 1267 mg/kg/day. LOAEL = not established.
870.3150	90-Day oral toxicity (Rat) – AMPA	00241351 (1979) Acceptable/guideline 0, 400, 1200, 4800 mg/kg/day [M/F]	NOAEL = 400 mg/kg/day [M/F]. LOAEL = 1200 mg/kg/day [M/F] based on body-weight loss and histopathological lesions of the urinary bladder.
870.3150	90-Day oral toxicity (Dog)- AMPA	43334702 0, 8.8, 26.4, 88, or 264 mg/kg/day	NOAEL= 264 mg/kg/day. LOAEL= not established. No toxicity at the highest dose tested.
870.3200	21-Day dermal toxicity (Rabbit)	00098460 (1982) Acceptable/guideline 0, 100, 1000, 5000 mg/kg/day	NOAEL = 1000 mg/kg/day in males and females. LOAEL = 5000 mg/kg/day based on slight erythema and edema on intact and abraded skin of both sexes, and decreased food consumption in females.
870.3465	28-Day inhalation toxicity (rat)	00137704 (1983) Acceptable/guideline 0, 0.05, 0.16, or 0.36 mg/L	NOAEL = 0.36 mg/L (HDT). LOAEL not established based on 6 hours/day, 5 days/week for 4 weeks.
870.3700a	Prenatal developmental in rodents (Rat)	00046362 (1980) Acceptable/guideline 0, 300, 1000, 3500 mg/kg/day via gavage during Gestation Days (GD) 6-19	**Maternal** NOAEL = 1000 mg/kg/day. LOAEL = 3500 mg/kg/day based on based on inactivity, mortality, stomach hemorrhages and reduced body-weight gain. **Developmental** NOAEL = 1000 mg/kg/day. LOAEL = 3500 mg/kg/day based on increased incidence in the number of fetuses and litters with unossified sternebrae and decreased fetal body weight.
870.3700a	Prenatal developmental in rodents (Rat)	44320615 (1996) Acceptable/guideline 0, 250, 500, or 1000 mg/kg/day via gavage during gestation days (GD) 6-15	**Maternal** NOAEL = 1000 mg/kg/day. LOAEL = not established. **Developmental** NOAEL = not established.
870.3700a	Prenatal developmental in rodents (Rat) - AMPA	43334705 (1991) Guideline 0, 150, 400, or 1000 mg/kg/day via gavage during GD 6-19	**Maternal** NOAEL = 150 mg/kg/day. LOAEL = 400 mg/kg/day based clinical signs (hair loss, soft stools and mucoid feces). **Developmental** NOAEL = 400 mg/kg/day. LOAEL = 1000 mg/kg/day based on decreased fetal body weight.
870.3700b	Prenatal developmental in (Rabbit)	00046363 (1980) Acceptable/guideline 0, 75, 175, or 350 mg/kg/day via gavage during GD 6-27	**Maternal** NOAEL = 75 mg/kg/day. LOAEL = 175 mg/kg/day based on based on mortality, diarrhea, soft stools, and nasal discharge. **Developmental** NOAEL = 350 mg/kg/day (HDT). LOAEL = not established.

Table B.3. Subchronic, Chronic, and Other Toxicity Profile.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b	Pre-natal Developmental Toxicity-Rabbit	(1996) Acceptable/guideline 44320616 0, 100, 175, or 300 day via gavage during GD7-19	Maternal NOAEL = 100 mg/kg/day. Maternal LOAEL = 175 mg/kg/day based on dose-dependent clinical signs (diarrhea, few/no feces). Developmental NOAEL = 300 mg/kg/day. Developmental LOAEL = not established.
870.3800	Reproduction and fertility effects, three-generation (Rat)	00105995 (1981) Acceptable/guideline 0, 3, 10, or 30 mg/kg/day in the diet.	**Parental/Systemic** NOAEL = 30 mg/kg/day (HDT). **Reproductive** NOAEL = 30 mg/kg/day (HDT). **Offspring** NOAEL = 10 mg/kg/day. LOAEL = 30 mg/kg/day based on focal dilation of the kidney in male F3b pups.
870.3800	Reproduction and fertility effects, two-generation (Rat)	41621501 (1990) Acceptable/guideline 0, 2000, 10,000, or 30,000 ppm (0, 250, 500, and 1500 mg/kg/day) in the diet.	**Parental/Systemic** NOAEL = 500 mg/kg/day in males and females. LOAEL = 1500 mg/kg/day in males and females based on soft stools, decreased body-weight gain and food consumption. Focal dilation of the kidney observed at 30 mg/kg/day in the three-generation study was not observed at any dose level in this study. **Reproductive** NOAEL = 1500 mg/kg/day (HDT) in males and females. **Offspring** NOAEL = 500 mg/kg/day in males and females. LOAEL = 1500 mg/kg/day in males and females based on decreased body-weight gain during lactation.
870.3800	Reproduction and fertility effects, two-generation (Rat)	48865101 (2012) Acceptable/guideline 0, 1500, 5000, or 15,000 ppm (0/0, 121/126, 408/423, or 1234/1273 mg/kg/day [M/F]) in the diet	**Parental/Systemic** NOAEL = 1234/1273 mg/kg/day in males and females. The LOAEL for parental toxicity was not observed. **Reproductive** NOAEL = 1234/1273 mg/kg/day (HDT) in males and females. **Offspring** NOAEL = 408/423 mg/kg/day in males and females. LOAEL = 1234/1273 mg/kg/day in males and females based on delayed age and increased weight at attainment of PPS.
870.4100a	Chronic toxicity (dog)	00153374 (1985) Acceptable/guideline 0, 20, 100, or 500 mg/kg/day [M/F] via gelatin capsule	NOAEL = 500 mg/kg/day [M/F]. LOAEL = not established.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	00093879 (1981) Minimum 0, 3, 10, or 34 mg/kg/day in the diet	NOAEL = 34 mg/kg/day. LOAEL = not established. High dose not adequate to assess carcinogenicity. Another study requested (see below).
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	41643801, 41728701 (1990) Acceptable/guideline 0, 2000, 8000, or 20000 ppm 0, 362/447, or 940/1183 mg/kg/day [M/F] in the diet.	NOAEL = 362/447 mg/kg/day [M/F]. LOAEL = 940/1183 mg/kg/day[M/F] based on decreased body-weight gain in females, decreased urinary pH in males, increased incidence of cataracts and lens abnormalities in males, and increased absolute and relative (to brain) liver weight in males.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	49631701 (1993) Acceptable/guideline 0, 10, 100, 300, or 1000 mg/kg/day [M/F] in the diet.	NOAEL=100 mg/kg bw/day [M/F]. LOAEL = 300 mg/kg bw/day [M/F] based on pronounced cellular alterations of the parotid and mandibular salivary glands.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	49704601 (2001) Acceptable/guideline 0, 2000, 6000, or 20,000 ppm 0,121/145, 361/437, and 1214/1498 mg/kg/day [M/F] in the diet.	NOAEL = 361/437 mg/kg bw/day [M/F]. LOAEL = 1214/1498 mg/kg bw/day [M/F] based on kidney papillary necrosis.

Table B.3. Subchronic, Chronic, and Other Toxicity Profile.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	40214007, 41209905, 41209907 (1987) Acceptable/guideline 0, 100, 500, and 1000 ppm 0, 4.2/5.4, 21.2/27 or 41.8/55.7 mg/kg/day [M/F] in the diet.	NOAEL = 100 ppm (4.2/5.4 mg/kg/day [M/F]) LOAEL = 500 ppm (21.2/27.0 mg/kg/day [M/F) based upon decreased LDH levels at 6 and 12 months.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	49987401 (1994) Acceptable/guideline 0, 6.3/8.6, 59.4/88.5, and 595.2/886 mg/kg/day [M/F] in the diet.	NOAEL ≥ 10,000 ppm (740.6 mg/kg/day) A LOAEL was not established.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	50017103, 50017104, 50017105 (1997) Acceptable/guideline 0, 3000, 10000, or 30000 ppm 0, 104/115, 354/393 and 1127/1247 mg/kg bw/day [M/F] in the diet.	NOAEL = 3000 ppm (104/115 mg/kg/day) LOAEL = 10000 ppm (354/393 mg/kg/day) based upon retarded growth in males throughout the study.
870.4200	Combined Chronic Toxicity/Carcinogenicity (Rat)	49957404 (2009) Acceptable/guideline 0, 1500, 5000, and 15,000 ppm 0, 86/105, 285/349 or 1077/1382 mg/kg/day [M/F] in the diet.	NOAEL is ≥ 1077/1382 mg/kg/day. A LOAEL was not established. Transient liver enzyme activity for mid-dose males and high-dose males and females were observed, in addition to increased adipose infiltration of the bone marrow in high-dose males. Both effects were not considered adverse.
870.4300	Carcinogenicity (Mouse)	00130406 (1983) Acceptable/guideline 0, 1000, 5000, or 30,000 ppm 0, 161/195, 835/968, 4945/6069 mg/kg bw/day [M/F] in the diet.	NOAEL = 835/968 mg/kg bw/day [M/F]. LOAEL = 4945/6069 mg/kg bw/day [M/F] based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females.
870.4300	Carcinogenicity (Mouse)	41643801, 41728701 (1990) Acceptable/guideline 0, 1000, 5000, or 30000 ppm 0, 150, 750, or 4500 mg/kg/day [M/F] in the diet.	NOAEL = 750 mg/kg/day [M/F]. LOAEL = 4500 mg/kg/day [M/F] based on significant decreased body-weight gain in both sexes, hepatocyte necrosis and interstitial nephritis in males, and increased incidence of proximal tubule epithelial basophilia and hypertrophy in the kidney of females.
870.4300	Carcinogenicity (Mouse)	49631702 (1993) Acceptable/guideline 0, 98/102, 297/298, 988/1000 mg/kg bw/day [M/F] in the diet.	NOAEL = 1000 mg/kg bw/day. A LOAEL was not identified.
870.4300	Carcinogenicity (Mouse)	49957402 (2009) Acceptable/guideline 0, 500, 1500, or 5000 ppm 0, 71.4/97.9, 234.2/299.5, or 810/1081.2 mg/kg bw/day [M/F] in the diet.	NOAEL ≥ 5000 ppm (234.2/299.5 mg/kg/day) A LOAEL was not established.

Table B.3. Subchronic, Chronic, and Other Toxicity Profile.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300	Carcinogenicity (Mouse)	50017108, 50017109 (1997) Acceptable/guideline 0, 1600, 8000, or 40000 ppm 0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg bw/day [M/F] in the diet.	NOAEL = 8000/1600 ppm (838.1/153.2 mg/kg/day [M/F]) LOAEL = 40000 ppm (4116 mg/kg/day [M]) based on a significant increase in overall incidence of anal prolapse which corresponded to erosion/ulcer of the anus histopathologically. LOAEL = 8000 (838.1 mg/kg/day [F]) based upon retarded growth with statistically significant decreases in weight at week 6 and weeks 9-24.
870.4300	Carcinogenicity (Mouse)	40214006, 41209907 (1987) Acceptable/guideline 0, 11.7/16, 118/159, and 991/1341 mg/kg bw/day [M/F] in the diet.	NOAEL = 1000 ppm (11.7/16 mg/kg/day [M/F]) LOAEL = 8000 ppm (118/159 mg/kg/day [M/F) based upon an increased incidence of white matter degeneration in the lumbar region of the spinal cord in males, and an increased incidence of epithelial hyperplasia of the duodenum in females. .
870.6200a	Acute neurotoxicity screening battery	44320610 (1996) Acceptable/guideline 0, 500, 1000, 2000 mg/kg [M/F]	Neurotoxicity NOAEL = 2000 mg/kg/day [M/F]. Neurotoxicity LOAEL was not observed. Systemic NOAEL = 2000 mg/kg/day [M/F]. Systemic LOAEL was not observed.
870.6200b	Subchronic neurotoxicity screening battery	44320612 (1996) Acceptable/guideline 0, 2000, 8000, 20000 ppm (0, 155.5/ 166.3, 617.1/672.1, 1546.5/1630.6 mg/kg/day [M/F])	Neurotoxicity NOAEL = 1546.5/1630.6 mg/kg/day [M/F]. Neurotoxicity LOAEL was not observed. Systemic NOAEL = 1546.5/1630.6 mg/kg/day [M/F]. Systemic LOAEL was not observed.
870.7800	Immunotoxicity (Mouse)	48934207 (2012) Acceptable/guideline 0, 500, 1500, 5000 ppm (0, 150, 499, 1448 mg/kg/day [F])	Immunotoxicity NOAEL = 1448 mg/kg/day. Immunotoxicity LOAEL was not observed. Systemic NOAEL = 1448 mg/kg/day. Systemic LOAEL was not observed.

1- The entire battery of additional metabolism, genotoxicity and mutagenicity studies considered by EPA can be found in the *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs, 2016.*

Table B.4 Acute, Subchronic, and Other Toxicity Profile for *N*-Acetyl-Glyphosate

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.1100 (*N*-Acetyl-Glyphosate)	Acute Oral Toxicity (Rat)	47007901 (2004) Acceptable/guideline 5000 mg/kg [M/F]	LD_{50} = greater than 5000 mg/kg in male and female rats.
870.3100 (*N*-Acetyl-Glyphosate)	90-Day oral toxicity (Rat)	47119201 (2007) Acceptable/guideline 0, 180, 900, 4500, and 18,000 ppm M: 0, 11.3, 55.7, 283, and 1157 mg/kg/day F: 0, 13.9, 67.8, 360, and 1461 mg/kg/day	NOAEL = 1157/1461 mg/kg/day (m/f), highest dose tested. LOAEL = was not established.
870.5100	Bacterial Gene Mutation	47007905 (2004) Acceptable/guideline 0, 100, 333, 1000, and 5000 µg/ per plate	Non-mutagenic when tested up to 5000 ug/plate, in presence and absence of activation in S. *typhimurium* strains TA100, TA1535 and TA1537 and in Escheria coli strain WP2urvA.

Table B.4 Acute, Subchronic, and Other Toxicity Profile for *N*-Acetyl-Glyphosate

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5300	In Vitro Mammalian Gene Mutation Test (CHO/HGPRT)	47007902 (2006) Acceptable/guideline 0, 250, 500, 1000, 1500, and 2091 µg/ml	Non-mutagenic at the HGPRT locus in Chinese hamster ovary cells tested up to 2091 µl/ml, in presence and absence of metabolic activation.
870.5300	*In vitro* Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) cells	47007903 (2004) Acceptable/guideline 0, 19.0, 27.1, 38.8, 55.4, 79.1, 113, 161, 231, 329, 471, 672, 960, 1370, 1960, and 2800 µg/ml ± S9 0, 960, 1370, 1960, and 2800 µg/ml – S9	No evidence of chromosomal aberration in Chinese Hamster Ovary cells when tested at doses up to 2800 µg/mL with or without metabolic activations.
870.5395	Mouse Bone Marrow Micronucleus Test	47007904 (2006) Acceptable/guideline 0, 500, 1000, 2000 mg/kg [M/F] 30 mg/kg Cyclophosphamide	No chromosomal aberrations were detected in male and female mice at doses up to 2000 mg/kg.
870.7485	Metabolism and pharmacokinetics (Rat)	47007906 (2004) Acceptable/guideline 15 mg free acid equivalent/kg	Absorption was estimated to be approximately 66% of the administered dose as estimated based on urinary excretion. The mean maximum concentrations in blood and plasma were 2.93 and 5.31 µg equiv./g at 1 and 2 hours post-dose, respectively. The half-life was 20.1 h in blood and 15.6 h in plasma. After 168 h post-dose, only 0.2% of the dose remained in the carcass, and 2.8% of the dose was isolated in the cage wash and wipe. A total of 97.25% of the dose was identified, and 97.18% of the dose was identified as parent. The remaining 0.07% of the identified dose was glyphosate, isolated in the feces. In the plasma, 100% of the sample radioactivity was identified as the parent. Similarly, 99.3-100% of the radiolabeled compounds from each sample was identified as parent in the urine and feces

Attachment C: HED-Recommended Tolerances and International Residue Limits

HED evaluated the glyphosate residue chemistry database to determine if the established tolerances conform to the current practices and to determine if the crop group/subgroup tolerances could be updated to the current crop group/subgroup definitions. Based on this analysis, HED is recommending for establishment of the tolerances listed in Table C.1. With the establishment of these tolerances, the following tolerances should be deleted: acerola; aloe vera; ambarella; asparagus; atemoya; avocado; bamboo, shoots; banana; biriba; breadfruit; cactus, fruit; cactus, pads; canistel; cherimoya; custard apple; date, dried fruit; durian; feijoa; fig; fruit, stone, group 12; guava; ilama; imbe; imbu; jaboticaba; jackfruit; longan; lychee; mamey apple; mango; mangosteen; marmaladebox; noni; nut, tree, group 14; olive; palm heart; papaya; papaya, mountain; passionfruit; pawpaw; persimmon; pineapple; pistachio; pomegranate; pulasan; rambutan; rose apple; sapodilla; sapote, black; sapote, mamey; sapote, white; soursop; Spanish lime; star apple; starfruit; sugar apple; Surinam cherry; tamarind; vegetable, leafy, brassica, group 5; vegetable, leafy, except brassica, group 4; watercress, upland; and wax jambu.

Table C.2 is a summary of the U.S. tolerances and the Canadian and Codex MRLs. For the majority of the crops, the U.S. and Codex residue definitions are identical. However, the Canadian residue definition differs in that it includes AMPA and N-acetyl-AMPA. Since the U.S. and Canadian residue definitions differ, harmonization of the tolerance value is irrelevant.

HED has evaluated the Codex MRLs and the U.S. tolerance to determine if harmonization is appropriate. HED determined that harmonization of the forage, fodder, and hay tolerances are unnecessary as these commodities are not important in terms of international trade. For the remaining commodities where there are both U.S. and Codex tolerances, HED determined that harmonization was either inappropriate as the Codex MRL is too high and would not be an adequate measure of misuse (sugar beet and popcorn) or the available residue data resulted in residues higher than the current Codex MRL (banana, sweet corn, sunflower seed, dry pea, dry bean, hog meat byproducts, poultry meat, and poultry meat byproducts).

Table C.1. HED Recommended Changes to the Tolerance Level or Commodity Definition.

Current		HED-Recommended		Comment
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)	
Soybean, forage	100.0	Soybean, forage	100	update to the current practice concerning significant figures
Soybean, hay	200.0	Soybean, hay	200	
Soybean, hulls	120.0	Soybean, hulls	120	
Soybean, seed	20.0	Soybean, seed	20	
Fruit, stone, group 12	0.2	Fruit, stone, group 12-12	0.2	update to the current crop group definitions; coconut was excluded from the tree nut crop group tolerances as the residues were not within 5x (coconut tolerance at 0.1 ppm)
Nut, tree, group 14	1.0	Nut, tree, group 14-12 (except coconut)	1.0	
Vegetable, leafy, except brassica, group 4	0.2	Vegetable, leafy, group 4-16	0.2	
Vegetable, leafy, brassica, group 5	0.2	Vegetable, *Brassica*, head and stem, group 5-16	0.2	
several	0.2-0.5--	Vegetable, stalk and stem, subgroup 22A	0.5	
	0.2	Vegetable, leaf petiole, subgroup 22B	0.2	
	0.2	Fruit, tropical and subtropical, edible peel, group 23	0.2	
	0.2	Fruit, tropical and subtropical, small fruit, inedible peel, group 24A	0.2	
	0.2	Fruit, tropical and subtropical, medium to large fruit,	0.2	

Table C.1. HED Recommended Changes to the Tolerance Level or Commodity Definition.

Current		HED-Recommended		Comment
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)	
		smooth, inedible peel, group 24B		
	0.2	Fruit, tropical and subtropical, large fruit, rough or hairy, inedible peel, group 24C	0.2	
	0.2	Fruit, tropical and subtropical, vine, inedible peel, group 24E	0.2	

Table C.2. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition[1]

US	Canada	Mexico[2]	Codex[3]
40 CFR §180.364 (a) All except livestock, canola, field corn, AGF, and soybean: glyphosate. livestock, canola, field corn, AGF, and soybean: glyphosate and N-acetyl-glyphosate (expressed as glyphosate)	All except livestock, dry soybeans, canola, and field corn: glyphosate and AMPA. Livestock, dry soybeans, canola, and field corn: glyphosate, AMPA, N-acetyl-AMPA (not include in the livestock MRLs), **and N**-acetyl-glyphosate.	--	All except soya bean and maize: glyphosate. Soya bean and Maize: glyphosate and N-acetyl-glyphosate (expressed as glyphosate).

Tolerance/MRL (ppm)

Commodity	US	Canada	Mexico[2]	Codex[3]
Alfalfa, seed	0.5	--	--	--
Almond, hulls	25	--	--	--
Animal feed, nongrass, group 18	400	--	--	--
Artichoke, globe	0.2	--	--	--
Barley, bran	30	10 barley	--	20 wheat bran, unprocessed
Beet, sugar, dried pulp	25	--	--	--
Beet, sugar, roots	10	10	--	15 sugar beet
Beet, sugar, tops	10	--	--	--
Berry and small fruit, group 13-07	0.2	--	--	--
Betelnut	1.0	--	--	--
Blimbe	0.2	--	--	--
Cacao bean, bean	0.2	--	--	--
Carrot	5.0	--	--	--
Chaya	1.0	--	--	--
Citrus, dried pulp	1.5	--	--	--
Coconut	0.1	--	--	--
Coffee, bean, green	1.0	--	--	--
Corn, pop, grain	0.1	3	--	5 maize
Corn, sweet, kernel plus cob with husk removed	3.5	3	--	3
Cotton, gin byproducts	210	--	--	--
Dokudami	2.0	--	--	--
Epazote	1.3	--	--	--
Fish	0.25	--	--	--
Fruit, citrus, group 10-10	0.5	--	--	--
Fruit, pome, group 11-10	0.2	--	--	--
Fruit, tropical and subtropical, edible peel, group 23	0.2	--	--	--
Fruit, tropical and subtropical, small fruit, inedible peel, group 24A	0.2	--	--	--
Fruit, tropical and subtropical, medium to large fruit, smooth, inedible peel, group 24B	0.2	banana - 0.05	--	--
Fruit, tropical and subtropical, large fruit, rough or hairy, inedible peel, group 24C	0.2	--	--	--
Fruit, tropical and subtropical, vine, inedible peel, group 2EA	0.2	--	--	--
Fruit, stone, group 12-12	0.2	--	--	--
Galangal, roots	0.2	--	--	--

Table C.2. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition[1]			
US	Canada	Mexico[2]	Codex[3]
40 CFR §180.364 (a) All except livestock, canola, field corn, AGF, and soybean: glyphosate. livestock, canola, field corn, AGF, and soybean: glyphosate and N-acetyl-glyphosate (expressed as glyphosate)	All except livestock, dry soybeans, canola, and field corn: glyphosate and AMPA. Livestock, dry soybeans, canola, and field corn: glyphosate, AMPA, N-acetyl-AMPA (not include in the livestock MRLs), **and N**-acetyl-glyphosate.	--	All except soya bean and maize: glyphosate. Soya bean and Maize: glyphosate and N-acetyl-glyphosate (expressed as glyphosate).

Tolerance/MRL (ppm)				
Commodity	US	Canada	Mexico[2]	Codex[3]
Ginger, white, flower	0.2	--	--	--
Gourd, buffalo, seed	0.1	--	--	--
Governor's plum	0.2	--	--	--
Gow kee, leaves	0.2	--	--	--
Grain, cereal, forage, fodder and straw, group 16, except field corn, forage and field corn, stover	100	--	--	400 barley straw and fodder, dry; 100 oat straw and fodder, dry; 50 sorghum straw and fodder, dry; 300 wheat straw and fodder, dry
Grain, cereal, group 15 except field corn, popcorn, rice, sweet corn, and wild rice	30	10 barley; 5 wheat; 15 oats; 15 barley, wheat (milling fractions, excluding flour); 35 oats milling fractions, excluding flour	--	30 cereal grains (except maize and rice)
Grass, forage, fodder and hay, group 17	300	--	--	500 hay or fodder (dry) of grasses
Herbs subgroup 19A	0.2	--	--	--
Hop, dried cones	7	--	--	--
Kava, roots	0.2	--	--	--
Kenaf, forage	200	--	--	--
Leucaena, forage	200	--	--	--
Mioga, flower	0.2	--	--	--
Nut, pine	1.0	--	--	--
Nut, tree, group 14-12 (except coconut)	1.0	--	--	--
Oilseeds, group 20, except canola	40	10 seeds (borage, cuphea, echium, gold of pleasure, hare's ear mustard, milkweed, mustard seed (condiment and oilseed type), oil radish, poppy seed, sesame, sweet rocket); 3 flax seed; 40 undelinted cotton seed	--	40 cotton seeds 7 sunflower seed
Okra	0.5	--	--	--
Oregano, Mexican, leaves	2.0	--	--	--
Palm heart, leaves	0.2	--	--	--
Palm, oil	0.1	--	--	--
Pea, dry	8.0	5 peas	--	5 peas (dry)
Peanut	0.1	--	--	--
Peanut, hay	0.5	--	--	--
Pepper leaf, fresh leaves	0.2	--	--	--
Peppermint, tops	200	--	--	--
Perilla, tops	1.8	--	--	--
Pistachio	1.0	--	--	--
Quinoa, grain	5.0	--	--	--
Rice, grain	0.1	--	--	--
Rice, wild, grain	0.1	--	--	--
Shellfish	3.0	--	--	--
Spearmint, tops	200	--	--	--
Spice subgroup 19B	7.0	--	--	--
Stevia, dried leaves	1.0	--	--	--
Sugarcane, cane	2.0	--	--	2
Sugarcane, molasses	30	--	--	10
Sweet potato	3.0	--	--	--
Tea, dried	1.0	--	--	--

Table C.2. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition[1]			
US	Canada	Mexico[2]	Codex[3]
40 CFR §180.364 (a) All except livestock, canola, field corn, AGF, and soybean: glyphosate. livestock, canola, field corn, AGF, and soybean: glyphosate and N-acetyl-glyphosate (expressed as glyphosate)	All except livestock, dry soybeans, canola, and field corn: glyphosate and AMPA. Livestock, dry soybeans, canola, and field corn: glyphosate, AMPA, N-acetyl-AMPA (not include in the livestock MRLs), **and N**-acetyl-glyphosate.	--	All except soya bean and maize: glyphosate. Soya bean and Maize: glyphosate and N-acetyl-glyphosate (expressed as glyphosate).

Tolerance/MRL (ppm)				
Commodity	US	Canada	Mexico[2]	Codex[3]
Tea, instant	7.0	--	--	--
Teff, forage	100	--	--	--
Teff, grain	5.0	--	--	--
Teff, hay	100	--	--	--
Ti, leaves	0.2	--	--	--
Ti, roots	0.2	--	--	--
Ugli fruit	0.5	--	--	--
Vegetable, bulb, group 3-07	0.2	--	--	--
Vegetable, *Brassica*, head and stem, group 5-16	0.2	--	--	--
Vegetable, cucurbit, group 9	0.5	--	--	--
Vegetable, foliage of legume, subgroup 7A, except soybean	0.2	--	--	200 bean fodder 500 pea hay or pea fodder (dry)
Vegetable, fruiting, group 8-10 (except okra)	0.1	--	--	--
Vegetable, leaf petiole, subgroup 22B	0.2	--	--	--
Vegetable, leafy, group 4-16	0.2	--	--	--
Vegetable, leaves of root and tuber, group 2, except sugar beet tops	0.2	--	--	--
Vegetable, legume, group 6 except soybean and dry pea	5.0	4 beans, dry lentils	--	2 beans (dry) 5 lentil (dry)
Vegetables, root and tuber, group 1, except carrot, sweet potato, and sugar beet	0.2	--	--	--
Vegetable, stalk and stem, subgroup 22A	0.5	asparagus - 0.5	--	--
Wasabi, roots	0.2	--	--	--
Water spinach, tops	0.2	--	--	--
Yacon, tuber	0.2	--	--	--
Canola, seed	20	20	--	30
Cattle, meat byproducts	5.0	2 kidney of cattle; 0.2 liver of cattle	--	5 edible offal mammalian
Corn, field, forage	13	--	--	--
Corn, field, grain	5.0	3	--	5 maize
Corn, field, stover	100	--	--	150 maize fodder (dry)
Egg	0.05	0.08	--	0.05*
Goat, meat byproducts	5.0	2 kidney of goats; 0.2 liver of goats	--	5 edible offal mammalian
Grain aspirated fractions	310	--	--	--
Hog, meat byproducts	5.0	2 kidney of hogs; 0.2 liver of hogs	--	5 pig, edible offal of
Horse, meat byproducts	5.0	2 kidney of horses; 0.2 liver of horses	--	5 edible offal mammalian
Poultry, meat	0.10	0.08	--	0.05*
Poultry, meat byproducts	1.0	2 kidney of poultry; 0.2 liver of poultry	--	0.5 poultry, edible offal of
Sheep, meat byproducts	5.0	2 kidney of sheep; 0.2 liver of sheep	--	5 edible offal mammalian
Soybean, forage	100	--	--	--
Soybean, hay	200	--	--	--
Soybean, hulls	120	--	--	--
Soybean, seed	20	20 dry soybeans	--	20 soya bean (dry)
MRLs with No US Equivalent				
Alfalfa fodder	--	--	--	500
Meat (from mammals other than marine mammals)	--	0.08 meat of (cattle, goats, hogs, horses, and sheep)	--	0.05*
Milk	--	0.08	--	0.05*

Table C.2. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition[1]			
US	Canada	Mexico[2]	Codex[3]
40 CFR §180.364 (a) All except livestock, canola, field corn, AGF, and soybean: glyphosate. livestock, canola, field corn, AGF, and soybean: glyphosate and N-acetyl-glyphosate (expressed as glyphosate)	All except livestock, dry soybeans, canola, and field corn: glyphosate and AMPA. Livestock, dry soybeans, canola, and field corn: glyphosate, AMPA, N-acetyl-AMPA (not include in the livestock MRLs), **and N**-acetyl-glyphosate.	--	All except soya bean and maize: glyphosate. Soya bean and Maize: glyphosate and N-acetyl-glyphosate (expressed as glyphosate).

Tolerance/MRL (ppm)				
Commodity	US	Canada	Mexico[2]	Codex[3]
Fat of (cattle, goats, hogs, horses, poultry and sheep)	--	0.15	--	--
Completed: M. Negussie; 08/31/15				

[1] glyphosate = *N*-(phosphonomethyl)glycine; N-acetyl-glyphosate = N-acetyl-N-(phosphonomethyl)glycine; AMPA = aminomethylphosphonic acid.
[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.
[3] * = absent at the limit of quantitation (LOQ); Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

Attachment D: Physicochemical Properties

The physicochemical properties of technical grade glyphosate are presented in Table D.1. Glyphosate is water soluble with a low Log Kow.

Table D.1. Physicochemical Properties of the Technical Grade Glyphosate.

Melting point	189.5 ± 0.5 °C	The Pesticide Manual, 13th Edition
pH	1.9 at 20 °C	
Density	1.705 g/cm^3 at 20 °C	
Water solubility	10.5 g/L at 20 °C	
Solvent solubility	acetone 0.078 g/L methanol 0.231 g/L hexane 0.026 g/L ethyl acetate 0.012 g/L dichloromethane 0.233 g/L n-octanol 0.020 g/L propan-2-ol 0.020 g/L toluene 0.036 g/L	European Commission: Glyphosate 6511/VI/99-final, 21-Jan-2002
Vapor pressure	1.31 x 10^{-2} mPa at 25 °C	The Pesticide Manual, 13th Edition
Dissociation constant, pK_a	0.8 (1st phosphonic), 2.3 (carboxylate), 6.0 (2nd phosphonic), and 11.0 (amine)	Knuuttila. 1979 Acta Chem. Scand. B 33:623-626
Octanol/water partition coefficient, Log(Kow)	-3.2 (pH 2-5, 25 °C)	European Commission: Glyphosate 6511/VI/99-final, 21-Jan-2002
UV/visible absorption spectrum	ε = 0.086 (295 nm)	

Attachment E: References

Tracking Code	Author	Date	Title
Risk Assessment and Scoping Documents			
D345923	P. Shah *et al.*	18-Mar-2008	Glyphosate-Isopropylammonium and Pyrithiobac Sodium. Human-Health Risk Assessment for Application to Glyphosate-Tolerant Soybean.
D362745	J. Van Alstine *et al.*	3-Jun-2009	Glyphosate. Human-Health Assessment Scoping Document in Support of Registration Review.
D369999	J. Van Alstine *et al.*	28-Dec-2009	Glyphosate. Public Comments Regarding the Health Effects Division's (HED's) Human-Health Assessment Scoping Document in Support of Registration Review of 3-JUN-2009. HED's Response to Public Comments.
D398547	T. Bloem *et al.*	14-Nov-2012	Glyphosate. Section 3 Registration Concerning the Application of Glyphosate to Carrots, Sweet Potato, Teff, and Oilseeds (Crop Group (CG) 20) and to Update the CG Definitions for Bulb Vegetable (CG 3-07), Fruiting Vegetable (CG 8-10), Citrus Fruit (CG 10-10), Pome Fruit (CG 11-10), and Berry (CG 13-07). Human-Health Risk Assessment.
Toxicology			
TXR No. 0056885	M. Perron	12-DEC-2017	Glyphosate: Literature Review
TXR No. 0057299	J. Rowland	10-01-2015	Evaluation of the Carcinogenic Potential of Glyphosate
--	OPP	12-Sep-2016	Glyphosate Issue Paper: Evaluation of Carcinogenic Potential
Incident Report			
D417808	S. Recore et al.	6-Feb-2014	Glyphosate: Tier II Incident Report
Dietary Exposure			
D440486	J. Hetrick	15-Jun-2017	Drinking Water Assessment for the Registration Review of Glyphosate.
D429229	T. Bloem	30-Nov-2017	Dietary Exposure Analysis in Support of Registration Review.
ACB Project B14-46	L. Podhorniak	18-Sep-2015	Analysis of Human Milk for Incurred Residues of Glyphosate and its Metabolites.
Residential Exposure			
D398862	L. Venkateshwara	30-Oct-2012	Glyphosate. Occupational and Residential Exposure Assessment for a Proposed Use on Carrots, Sweet Potato, Teff and Oilseeds (Harvest Aid).
Residue Chemistry			
D200041	G. Kramer	12-May-1994	Label Amendment for Roundup (Glyphosate)
D217539	G. Kramer	14-Mar-1996	Glyphosate in or on Corn Forage. Evaluation of Residue Data and Analytical Methods.
D242628	T. Bloem	30-Nov-1998	Glyphosate residues in/on glyphosate tolerant canola seed and canola meal. Amendment of 24-August-1998.
D346713	T. Bloem	12-Mar-2008	Glyphosate-Isopropylammonium and Pyrithiobac Sodium. Application to Glyphosate-Tolerant Soybeans. Summary of Analytical Chemistry and Residue Data.
D357880	T. Bloem	29-Oct-2008	Glyphosate and Pyrithiobac Sodium. Amended Section 3 Registration to Permit the Rotation to Glyphosate-Tolerant Field Corn and Glyphosate-Tolerant Soybean Following Application to Glyphosate-Tolerant Cotton and Revision of the Field Corn Tolerance Expression. Summary of Analytical Chemistry and Residue Data.
D361315	T. Bloem	14-Jan-2010	Glyphosate and Pyrithiobac Sodium in/on Glyphosate-Tolerant Soybean. Review of Amendment Dated 9-December-2008 Submitted in Response to Residue Chemistry Deficiencies Identified in D346713 (T. Bloem, 12-Mar-2008).
D394964	T. Bloem	15-Nov-2011	Glyphosate. Section 3 Registration for Application of the Isopropylamine Salt of Glyphosate to DuPont™ Optimum® GLY Canola. Summary of Analytical Chemistry and Residue Data.
Literature Studies			
--	A. Anadon	2009	Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats
--	D. Brewster	1991	Metabolism of Glyphosate in Sprague-Dawley Rats: Tissue Distribution, Identification, and Quantitation of Glyphosate-Derived Materials following a Single Oral Dose

Attachment F: Dietary Exposure Estimates Associated with Subsistence Fishing.

Glyphosate is registered for direct application to water with fish (0.25 ppm) and shellfish (3.0 ppm) tolerances established (180.364(a)(1)). Although these tolerances were incorporated into the dietary exposure analysis, the employed consumption database does not consider consumption levels associated with subsistence fishing. Making the conservative assumptions that an adult (69-kg body weight) or child (10-kg body weight) will consume on a chronic basis 200 grams/day or 25 grams/day, respectively, of fish and shellfish and assuming tolerance-level residues, the resulting exposure estimates are <1% of the cPAD. Therefore, exposure to glyphosate for individuals who consume fish/shellfish on a regular basis is not significantly different from that of the general population. The fish/shellfish consumption rates were attained from the State of Washington Department of Ecology Fish Consumption Rates Technical Support Document (Tables 1 and A.1).