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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: April 23, 2018

SUBJECT: Glyphosate: Response to Comments on the Human Health Draft Risk Assessment

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The Office of Pesticide Programs received thousands of public comments related to the human health draft risk assessment (DRA) for glyphosate in support of glyphosate's registration review. Comments addressing the human health risk assessment came from a wide array of stakeholders, including environmental non-governmental organizations (e.g., Natural Resource Defense Council, Center for Biological Diversity, Food & Water Watch, Environmental Working Group, Pesticide Action Network), consumer groups (e.g., Moms Across America, Environmental Action), pesticide registrants (e.g., the Joint Glyphosate Task Force, the Scotts Miracle-Gro Company), and private citizens (including anonymous commenters and growers). OPP has thoroughly reviewed all of the comments received during the public comment period. The Agency appreciates the substantial pubic interest in glyphosate. Due to the large volume of comments received on the risk assessment, the Agency identified the most detailed, substantive, and/or unique comments and addressed them as part of the identified "themes" below. Overall,

the comments received do not result in substantive changes to the Agency's human health risk assessment for glyphosate. EPA continues to conclude that exposure to glyphosate when used according to the label does not result in human health risk, including infants and children.

Cancer Assessment

- *Potential genotoxicity and carcinogenicity of glyphosate*
- *Consideration of Scientific Advisory Panel (SAP) recommendations*
- *Disagreement with International Agency for Research on Cancer (IARC) classification*
- *Weight of evidence evaluation of animal carcinogenicity data*

Several commenters expressed concern regarding the Agency's cancer assessment and disagreement with the Agency's cancer classification. Many of the commenters cited the IARC cancer classification of "probably carcinogenic to humans". The Agency conducted an independent evaluation of the cancer potential of glyphosate and concluded that glyphosate is "not likely to be carcinogenic to humans." This conclusion is based on a weight-of-evidence evaluation in accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment.

In December 2016, the Agency's evaluation of the human carcinogenic potential of glyphosate was presented to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) SAP for external peer review. This evaluation included an in-depth review of all relevant animal carcinogenicity and genotoxicity studies for the active ingredient glyphosate, as well as epidemiological studies that investigated potential carcinogenic effects from using pesticide products containing glyphosate. The epidemiological data was considered in this evaluation since it represents the best available data for evaluating human exposures and potential risk of cancer in the absence of epidemiological data on the active ingredient alone.

Although the panel did not reach complete consensus on several charge questions, none of the panel members believed glyphosate should be classified as "likely to be carcinogenic to humans" or "carcinogenic to humans". The Agency utilizes SAP reports as they represent the full continuum of opinions expressed. In the specific case of glyphosate, given the variety of opinions expressed, the Agency focused on statements where consensus appeared to be reached to revise the Issue Paper. The revised Issue Paper (D444689; TXR 0057688; G. Akerman; 12-DEC-2017) and a response to the SAP report (D444688; TXR 0057689; G. Akerman; 12-DEC-2017) along with associated supporting documents were released in December 2017[1].

Several public comments to the human health DRA were also received regarding the Agency's weight of evidence evaluation of the animal carcinogenicity data, including statistical evaluation, evaluation of preneoplastic and related non-neoplastic lesions, and use of historical controls. These comments have already been addressed in the response to the SAP report. Further information on the Agency's weight of evidence evaluation of the potential carcinogenicity of glyphosate can be found in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017).

[1] https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate

The Agency's conclusion that glyphosate is "not likely to be carcinogenic" is consistent with other countries and regulatory authorities/international organizations including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, European Food Safety Authority, the European Chemicals Agency, German Federal Institute for Occupational Safety and Health, The Joint FAO/WHO Meeting on Pesticide Residues, the New Zealand Environmental Protection Authority, and Food Safety Commission of Japan.

The Agency's analysis is more robust compared with IARC's evaluation. IARC considered a subset of the studies included in the Agency's evaluation. For instance, IARC only considered 8 animal carcinogenicity studies, while the Agency utilized 15 acceptable animal carcinogenicity studies in its evaluation. The Agency also did not use some studies that IARC incorporated into their evaluation because the studies were not appropriate for determining the human carcinogenic potential of glyphosate. For example, genotoxicity studies conducted in non-mammalian species (i.e., worms, fish, reptiles, plants) were excluded from the Agency's evaluation because they were not considered relevant for informing the genotoxic risk in humans. Furthermore, the Agency's process for evaluating the potential carcinogenicity of glyphosate is more transparent than IARC's process. As part of the SAP process, public participation is encouraged with the Agency's draft evaluation and all supporting documents provided in advance of the meeting, several opportunities available for oral and written public comments to be submitted, and the meeting was open to the public and available by webcast. The SAP meeting is well-documented with publication of a full transcript of the meeting and a final report drafted by SAP panel members. Additionally, the Agency drafted a response to the SAP report, which addressed the panel recommendations and identified revisions that were made in the Agency's Issue Paper following the SAP meeting. In contrast, IARC meetings are not accessible to the public. The committee deliberations are closed and the process does not allow for public comments to be submitted for consideration. Furthermore, there are no materials available in advance of the meeting, reports are final without any external peer review, and conclusions are not well described.

Glyphosate toxicological studies

- *Use and availability of industry generated studies*
- *The Agency should conduct search of open literature studies*
- *Chronic, developmental, reproductive, dermal, inhalation, neurotoxic, immunotoxic, and ocular effects*

Several commenters assert that the Agency relies too heavily on industry-funded studies and that these studies are not accessible to the public and requested the Agency to use open literature studies for the glyphosate hazard evaluation.

In the case of glyphosate, the Agency is aware of a significant number of studies published in the open literature. In 2012, the Office of Pesticide Programs (OPP) published a guidance document to provide guidance procedures for considering and using open literature toxicity studies to support human health risk assessment[2]. This guidance assists OPP scientists in their judgement of the scientific quality of open literature publications and has been applied in the glyphosate

[2] 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

review. More recently, 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[3]. 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"[4].

As part of the glyphosate registration review process, the Agency reviewed the open literature for hazard identification and characterization purposes in order to identify studies that could potentially impact the human health risk assessment. The first search was performed in late 2011/early 2012 and another search was performed in October 2015 using the concepts consistent with systematic review, such as detailed tracking of search terms and which literature have been included or excluded. The Agency also considered studies that were submitted by non-profit groups or members of the public as part of this 2015 review. These reviews are summarized in the DRA and a separate memo (D417703; TXR 0056885; M. Perron; 12-DEC-2017). Only a limited number of studies were deemed acceptable and appropriate for consideration in risk assessment. None of the studies were found to have an impact on the hazard characterization or draft human health risk assessment for glyphosate.

A fit-for-purpose systematic review was also executed to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate and reviewed by the SAP in 2016. This additional review identified numerous epidemiological and genotoxicity studies from the literature in addition to the guideline genotoxicity and animal carcinogenicity studies submitted to the Agency. Details regarding this review can be found in the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (D444689; TXR 0057688; G. Akerman; 12-DEC-2017).

Under FIFRA, the Agency requires substantial amounts of toxicology and exposure data to be collected and submitted for pesticide registration. These studies, defined under the Title 40 Code of Federal Regulations (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. In general, many of these studies are commissioned and submitted by the pesticide producers. To ensure data quality and consistency, the Agency has standard guidelines for how testing is to be conducted. The Agency's test guidelines are largely harmonized with those established by the Organisation for Economic Co-operation and Development (OECD). Harmonization also eases comparisons across studies and chemicals. Laboratories must also conduct studies in accordance with Good Laboratory Practices (GLP) standards (40 CFR Part 160) to further ensure the quality and integrity of the data submitted to the Agency. Study reports must include a statement on whether they were conducted in accordance with the GLP procedures. The Agency's Office of Enforcement and Compliance Assurance (OECA) periodically inspects labs that conduct studies to support pesticide registrations to ensure they are in compliance with GLPs.

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[3] 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"

[4] 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

Review of all studies submitted to the Agency's Office of Pesticide Programs (OPP) is a multi-step process. Test reports must summarize and supply all the individual data obtained as part of the study; most toxicity study reports are well over a thousand pages long. An independent evaluation is prepared for each study and a Data Evaluation Record (DER) is generated to summarize the study methods, results, and conclusions. Draft DERs are subject to an internal peer review process, including review by multiple individual scientists and scientific review committees within OPP, to ensure accuracy and consistency with Agency guidance on interpretation of toxicity studies prior to finalization.

Studies evaluated by the Agency are available to the public through Freedom of Information Act (FOIA) requests, however, section 10(g) of FIFRA prohibits the Agency from disclosing certain information submitted by an applicant or registrant to any representative of a multinational pesticide producer or anybody who intends to deliver such information to a multinational pesticide producer. In order to receive registrant submitted data/studies, Section 10(g) requires requestors to sign an Affirmation of Non-Multinational Status form[5]. The form affirms the person requesting the pesticide data does not work for or represent a pesticide producer. Section 10(g) also requires the Agency to notify the data owner to whom we released the data to. Please keep in mind that registrant-submitted studies are proprietary and cannot be posted or released for public access. For more information on how to submit FOIA requests to access certain glyphosate studies, visit the Agency's website: https://www.epa.gov/foia/foia-request-process.

The entire toxicity database available is used to identify and characterize the potential health effects of a pesticide. This includes acceptable studies submitted by registrants and open literature studies. Although numerous comments were received regarding concerns for a suite of non-cancer effects, including chronic toxicity, ocular effects, developmental toxicity, reproductive toxicity, dermal effects, inhalation effects, neurotoxicity, and immunotoxicity, the available studies indicate that glyphosate will not elicit these effects, or these effects would only be observed at relatively high doses. Numerous studies are available that evaluated chronic exposure to glyphosate in rats, mice, and dogs. In most instances, effects were only seen at or near the limit dose (1000 mg/kg/day). Developmental effects in rats were only observed at a dose exceeding the limit dose (3500 mg/kg/day) and there were no developmental effects observed in rabbits. Route-specific studies are available that evaluated dermal and inhalation exposures. Dermal irritation effects were only seen at a dose exceeding the limit dose (5000 mg/kg/day), which is well above exposures expected from glyphosate use and not relevant for human health risk assessment. There were no effects observed in the inhalation study up to a dose approaching the limit concentration (0.36 mg/L). There was no evidence in the toxicological databases that glyphosate would cause ocular effects, reproductive effects, neurotoxicity, or immunotoxicity, including the guideline neurotoxicity battery, reproductive toxicity and immunotoxicity studies. Overall, the selected endpoints for risk assessment are protective of all adverse effects observed in the database.

Endocrine disruption

Some commenters assert that glyphosate is an endocrine disruptor based on open literature studies conducted primarily with commercial formulations containing glyphosate. For the few

[5] http://www2.epa.gov/foia/affirmation-non-multinational-status

studies that evaluated glyphosate alone, there were no clear endocrine-related effects observed. Glyphosate was screened under the Agency's Endocrine Disruptor Screening Program (EDSP). Under the program, a suite of Tier 1 *in vivo* and *in vitro* studies was required for glyphosate that were designed to provide the necessary empirical data to evaluate the potential of glyphosate to interact with the estrogen, androgen, or thyroid signaling pathways. In addition to the available Tier 1 assay data, other scientifically relevant information, including general toxicity data and open literature studies of sufficient quality, are considered in the Agency's weight of evidence assessment. Based on all available information, the Agency concluded using a weight of evidence approach that the existing data do not indicate that glyphosate has the potential to interact with the estrogen, androgen, or thyroid signaling pathways (TXR 0057175; G. Akerman; 29-JUN-2015)[6].

Protection of children

Several commenters assert that the Agency is not being protective of children. The Agency places top priority on the safety of children exposed to pesticides in food and/or water and living in or near areas treated with pesticides. The Food Quality Protection Act (FQPA) requires the Agency to give specific consideration to the potential for infants and children to be sensitive to pesticides[7]. Based on the 40 CFR Part 158 data requirements, pesticides typically have toxicology studies to evaluate effects in pregnant animals and their fetuses and young rats up through adulthood. Developmental and multi-generation reproduction studies are used to evaluate the potential effects of a pesticide on fetuses and offspring. Developmental studies are used to determine whether gestational exposure has an effect on the developing fetus. Multi-generation reproduction studies are used to evaluate parental and offspring toxicity, as well as reproductive toxicity, from long-term exposure to a pesticide. This includes exposure during gestation and lactation. The results of these studies are considered as part of the entire toxicity database to ensure doses selected for risk assessment are protective of any potential fetal and offspring effects.

Typical food-use pesticides have two developmental toxicity studies (one with rats and one with rabbits) and one study evaluating reproductive toxicity. In the case of glyphosate, there are 2 rat developmental, 2 rabbit developmental, and 3 reproductive toxicity studies available. The Agency found no indication that offspring are more sensitive to glyphosate from *in utero* or post-natal exposure in any of these studies. Additionally, any developmental or offspring effects were seen at doses much higher than those used for risk assessment. As part of the human health DRA to support registration review, the Agency evaluates all populations, including infants, children, and women of child-bearing age. There were no risks of concern identified for children from ingesting food/feed commodities or from entering/playing on residential areas treated with glyphosate using conservative assumptions to calculate high-end exposure estimates. Furthermore, in accordance with FQPA, aggregate exposures and risks from food, drinking

6 Available at https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and

7 HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

water, and residential exposures were calculated for adults and children. There were no aggregate risks of concern. The Agency's current risk assessment is protective of children.

Detection of glyphosate in human milk, tissues, and urine

Many commenters cite reports of glyphosate detections in human milk, tissues, and urine. The Agency has identified several issues with studies claiming to detect glyphosate in urine, tissues, and human milk. Among the key information missing from such studies are the information related to sampling methods, sample storage, sample shipping, quality assurance and quality control, and analytical methods used, which are critical to evaluating the reliability of the data. Additionally, the enzyme-linked immunosorbent assay (ELISA) method is often used in the tests. This method is known to work well with surface waters that have little or no suspended solids or with processed drinking water. However, many of the samples in these cited tests would have significant amounts of dissolved solids which may lead to issues when using the ELISA method with these sample types. Furthermore, the ELISA method is generally considered to be a semi-quantitative method that is typically used as a screening or initial test method to determine the potential presence of a chemical. The results from such a method, therefore, do not provide data that can be used quantitively for human health risk assessment.

Glyphosate is not expected to accumulate in human milk and tissues. The Agency is not aware of any peer-reviewed studies reporting detection of glyphosate in human breast milk and, due to its physicochemical properties, glyphosate is not expected to bioaccumulate in the human body. Additionally, as noted in the DRA, the Agency Biological and Economic Analysis Division (BEAD) analyzed human milk samples in response to concern from segments of the general public related to the presence of glyphosate in human milk. Glyphosate, *N*-acetyl-glyphosate, and aminomethyl phosphonic acid (AMPA) were not detected in any of the human milk samples. On the other hand, detection of trace amounts of glyphosate in urine would be expected given the chemical does not bioaccumulate and is primarily excreted un-metabolized as glyphosate by mammals. Such trace levels of glyphosate are not of concern to the Agency since the corresponding body burden (or approximate magnitude of exposure in mg/kg body weight) assuming complete excretion of the absorbed amount and virtually no metabolism, would still be well below current regulatory levels[8].

Formulations*:*

- *Toxicity of inert compounds*
- *Transparency of components*
- *Contaminants in pesticide products*

Several commenters expressed concern that glyphosate formulations are more toxic than glyphosate alone and question the toxicity of inert ingredients, the lack of transparency around other ingredients in product formulations, and other contaminants in pesticide products. Most pesticide products contain substances in addition to the active ingredient(s) that are often referred to as inert or other ingredients, which aid in the performance and effectiveness of the pesticidal

8 Niemann et al. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. Journal of Consumer Protection and Food Safety. 10: 3-12.

product. Federal law does not require that these ingredients be identified by name or percentage on the label. In accordance with FIFRA, the Agency cannot disclose this information since these ingredients are considered trade secrets or confidential business information.

All active and inert pesticide ingredients must be approved for use by the Agency. The Agency carefully evaluates the active and inert components hazard potential (i.e., toxicity) of a pesticide product with a battery of appropriate toxicity data. However, there are tens of thousands of different registered pesticide products available in the marketplace and, though the Agency evaluates the product components, long term testing of individual products is not required. Any contaminants or impurities associated with formulation components need to be reported to the Agency and are evaluated on a case by case basis. The Agency looks at the amount of the impurity in the formulation, the manufacturing information, and what steps are taken to limit or remove impurities. A comment was received regarding formation of nitrosamines, which have been found to cause cancer. Technical grade glyphosate contains minor amounts of a nitrosamine impurity, N-nitrosoglyphosate (NNG). This contaminant was considered previously as part of the Reregistration Eligibility Decision (RED)[9]. Carcinogenicity testing of nitroso contaminants is normally required only in cases which the level of nitroso compounds exceeds 1.0 ppm. Analyses showed that greater than 92% of the individual technical glyphosate samples contained less than 1.0 ppm. No new data have been presented to warrant a reevaluation of the Agency's conclusion that the NNG content of glyphosate is not toxicologically significant.

Glyphosate has been studied in a multitude of studies and there are studies that have been conducted on numerous formulations that contain glyphosate; however, there are relatively few research projects that have attempted to directly compare glyphosate to the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations. The majority of studies using commercial formulations identified as part of the systematic review are *in vitro* studies, which are difficult to translate into *in vivo* effects where metabolism and clearance would play a large role in potential toxicity. Consequently, *in vivo* studies are given more weight. In the systematic review (D417703; TXR 0056885; M. Perron; 12-DEC-2017), none of the *in vivo* studies with commercial formulations were found to be of adequate quality for use in human health risk assessment. Common limitations/deficiencies seen in these studies included lack of test material information, exposure conditions were not adequately described or documented, data were only presented as graphs and often measures of variability were not included, samples sizes were too small for the type of study conducted and/or not reported for all lifestages, only one dose was tested, and age and overall health prior to commencing a study was not reported. Furthermore, most of these studies focused on clinical chemistry measurements (i.e., enzymes, hormones, electrolytes) or histopathological examinations (without reporting severity) making it difficult to determine the adversity of the results. The relationship between any changes noted in these effects and possible adverse apical outcomes from commercial formulations has not been established. As described in the NRC report, "Toxicity Testing in the 21st Century"[10], to develop a mode of action/adverse outcome pathway (MOA/AOP) not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established. In

[9] https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf

[10] National Research Council (NRC). 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, D.C. The National Academies Press.

other words, how much of a change in one key event is needed to result in an adverse effect at the next level of biological organization? Thus, certain exposures to a chemical may impact normal physiological responses in a way that may not necessarily be adverse, and thus, the MOA/AOP concept requires an understanding of adaptive/homeostatic capacity of biological systems and their limits, relative to concentration and duration of exposure. Without an MOA/AOP understanding or even a potentially solid hypothesis, pertubations in physiology cannot be interpreted for risk assessment without understanding how these changes lead to adverse outcomes.

The Agency has been collaborating with the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences to develop a research plan intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity. The results of this research will be considered when available.

Antibacterial properties and disruption of the gut microbiome

Many commenters assert that glyphosate has antibacterial properties and claim it contributes to antibiotic resistance and disruption of the gut microbiome. The metabolic pathway inhibited in plants by glyphosate (Shikimate pathway) is also found in many microorganisms. Although glyphosate may inhibit the Shikimate pathway in microorganisms, it has not been demonstrated to be an effective antimicrobial for treating humans. It is particularly difficult to achieve and maintain a sufficiently high concentration of glyphosate in the body to be an effective antimicrobial agent due to the low absorption and metabolism of glyphosate. Furthermore, although glyphosate may inhibit the production of certain amino acids in bacteria, these amino acids can be acquired from the body, when needed. Therefore, the inhibition does not necessarily lead to bacterial death.

Gut microbiomes (colonies of microbes in the gut) are unlikely to be altered from glyphosate exposure since the aromatic amino acids produced via the Shikimate pathway are also available in the human gut via the diet since humans are unable to synthesize them. Therefore, despite inhibition of this metabolic pathway, the microorganisms are still capable of growing and surviving. It has been suggested that glyphosate preferentially affects only "good" bacteria; however, this implies that microbes are defined by this metabolic pathway, which is not scientifically supported. Gut microbiomes are not evaluated directly in guideline toxicity studies; however, the stomach and gastrointestinal tract are routinely examined in several studies by gross evaluation and histopathological investigations. There are no indications in these studies that exposure to glyphosate induces adverse effects in those organs.

Metal chelation and nutritional deficiencies

Some commenters indicated that glyphosate is a metal chelator and consequently claim that it causes nutritional deficiencies. Glyphosate chelates with some metals in soil and aquatic environments. The relative proportion of the various chemical species of glyphosate (including dissociated species of glyphosate acid and glyphosate-metal complexes) is dependent on chemical characteristics (*e.g.*, pH, redox potential, etc.) of the environment. The Agency is unaware of any connection between metal chelation and toxicity of glyphosate in mammals. In

guideline studies for human health, exposure to glyphosate did not result in any changes in clinical or blood chemistry measurements, suggesting that glyphosate-metal chelation does not play a significant role in affecting human health.

Dietary Assessment

- *Residues in food and beverages*
- *Assessment of the dessicant use on wheat*

Many commenters point to reports of glyphosate residues being detected in food/beverage commodities such as honey, cereals, wine, and orange juice and expressed concerns about consumer safety. Due to its widespread use, trace amounts of glyphosate residues may be found in various food and beverage commodities. However, these trace amounts are not of concern to the consumer as the residue levels are well below tolerance levels established in/on food commodities treated with glyphosate. For example, the Agency has received information on glyphosate residues reported in orange juice at a maximum of 26 ppb. At this concentration, a 10 kg child would have to consume approximately 385 liters (1627 servings of an 8 oz glass) of orange juice every day to reach the chronic reference dose of 1 mg/kg/day.

As part of the human health risk assessment, the Agency evaluated dietary exposure to glyphosate for all populations, including infants, children, and women of child-bearing age. There were no dietary risks of concern for glyphosate using an unrefined analysis, which assumes all food commodities contain tolerance level residues (i.e., maximum legal residues allowed on a food commodity) of glyphosate, all food (with registered uses) has been treated with glyphosate, and using high-end estimates of glyphosate in drinking water.

Other commenters pointed to the use of glyphosate as a pre-harvest desiccant for wheat as a source of glyphosate residues in cereal products. Since the dietary exposure assessment was unrefined (assumed tolerance level residues and 100% crop treated) and the current tolerances reflect all registered uses, the wheat desiccant use was considered in the dietary analysis conducted as part of the human health DRA for registration review and there were no dietary risks of concern.

Non-Cancer Diseases

Several commenters expressed concern about the alleged link between exposure to glyphosate and various non-cancer diseases. In several instances, commenters noted a correlation in glyphosate use and some diseases; however, correlation does not imply causation. Increased prevalence of a disease may be due to many possible causes and verifying these causes should not be based on speculation. Determining whether an observed association represents a cause-effect relationship between glyphosate exposure and disease requires additional consideration of criteria, such as the modified Bradford-Hill criteria, that evaluate strength, consistency, dose response, temporal concordance and biological plausibility across multiple lines of evidence. Additionally, the plant MOA/AOP is not relevant for mammalian systems and there is a distinct lack of mechanistic understanding for the toxicity of glyphosate in mammals, which is used to inform the cause-effect relationship. As part of the Tier II Incident Report for glyphosate

(D417808; S. Recore; 6-FEB-2014;), an open literature search was conducted to identify epidemiological studies that evaluated the potential role of glyphosate and disease outcomes. The Agency reviewed studies related to a range of non-cancer effects, including adverse birth outcomes, respiratory effects, rheumatoid arthritis, diabetes, myocardial infarction, Parkinson's disease, and retinal degeneration. Most of the studies were not designed to develop data on non-cancer outcomes that could be used quantitatively or qualitatively in regulatory decision-making, but were more exploratory in nature. Additionally, in most instances, only one study was available for a specific outcome, which makes it challenging to assess consistency in the human population. Based on the available studies, the Agency could not conclude that glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. The Agency also examined journal articles regarding non-cancer disease outcomes submitted with comments to the DRA to identify any epidemiological studies that were not considered as part of the Tier II report. At this time, the available scientific data do not support a cause-and-effect relationship between exposure to glyphosate and any non-cancer disease outcomes. The Agency will continue to follow the epidemiological literature concerning the potential role of glyphosate in certain non-cancer health outcomes.