Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential

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List of Acronyms

ADME: Absorption, Distribution, Metabolism, and Excretion
AHS: Agricultural Health Study
AOP: Adverse Outcome Pathway
AMPA: Aminomethylphosphonic Acid
BrdU: Bromodeoxyuridine
CA: Chromosomal Aberration
CARC: Cancer Assessment Review Committee
CBPI: Cytokinesis Block Proliferation Index
CHL: Chinese Hamster Lung
CHO: Chinese Hamster Ovary
CPRC: Carcinogenicity Peer Review Committee
EFSA: European Food Safety Authority
EPSPS: 5-enolpyruvylshikimate-3-phosphate synthase
FAO: Food and Agriculture Organization
FIFRA: Federal Insecticide, Fungicide, and Rodenticide Act
FISH: Fluorescence *in situ* Hybridization
GC-MS: Gas Chromatography-Mass Spectrometry
HL: Hodgkin Lymphoma
HPLC: High-Performance Liquid Chromatography
HPRT: Hypoxanthine-Guanine Phosphoribosyl Transferase
IARC: International Agency for Research on Cancer
JMPR: Joint FAOWHO Meeting on Pesticide Residues
MGUS: Monoclonal Gammopathy of Undetermined Significance
MN: Micronuclei
MOA: Mode of Action
MPCE: Micronucleated Polychromatic Erythrocytes
MRID: Master Record Identifier (a unique number assigned to each study submitted to EPA)
MTD: Maximum Tolerated Dose
NB: Nuclear Bud
NCR: National Research Council
NHL: Non-Hodgkin Lymphoma
NPB: Nucleoplasmic Bridges
NTP: National Toxicology Program
OCSPP: Office of Chemical Safety and Pollution Prevention
OECD: Organization for Economic Cooperation and Development
OPP: Office of Pesticides Program
PCE: Polychromatic Erythrocytes
PK: Pharmacokinetic
PPE: Personal Protective Equipment
PWG: Pathology Work Group
RED: Registration Eligibility Decision
ROS: Reactive Oxygen Species
SAP: Scientific Advisory Panel
SCE: Sister Chromatid Exchange

SCGE: Single Cell Gel Electrophoresis
TAC: Total Antioxidant Capacity
TK: Thymidine Kinase
UDS: Unscheduled DNA Synthesis
USGS: United States Geological Survey
UV: Ultraviolet
WHO: World Health Organization
XPRT: Xanthine-Guanine Phosphoribosyl Transferase

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1.0 Introduction

1.1 Background

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. The herbicide acts by inhibiting the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme, which is not present in mammalian systems. Glyphosate was initially registered in 1974. Since then, several human health analyses have been completed for glyphosate. In 1986, EPA issued the Glyphosate Registration Standard which updated the agency's toxicity database for this compound. In 1993, EPA issued the registration eligibility decision (RED) that indicated that glyphosate was eligible for re-registration.

Currently, glyphosate is undergoing Registration Review[1], a program where all registered pesticides are reviewed at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The initial docket opening for glyphosate occurred in 2009 with the publication of the human health scoping document and preliminary work plan[2]. As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health. Risks are assessed using current practices and policies to ensure pesticide products can still be used safely. Registration Review also allows the agency to incorporate new science. For human health risk assessment, both non-cancer and cancer effects are evaluated for glyphosate and its metabolites, aminomethylphosphonic acid (AMPA) and *N*-acetyl-glyphosate; however, this document will focus on the cancer effects only. EPA expects to complete its complete human health risk assessment in 2017 that will include an assessment of risk from anticipated exposures resulting from registered uses of glyphosate in residential and occupational settings.

1.2 Evaluation of Carcinogenic Potential

Since its registration, the carcinogenic potential of glyphosate has been evaluated by EPA several times. In 1985, the initial peer review of glyphosate was conducted in accordance with the Proposed Guidelines for Carcinogen Risk Assessment. The agency classified glyphosate as a Group C chemical (Possible Human Carcinogen), based on the presence of kidney tumors in male mice. In 1986, the agency requested that the FIFRA Scientific Advisory Panel (SAP) evaluate the carcinogenic potential of glyphosate. The panel determined that the data on renal tumors in male mice were equivocal (only an increase in adenomas was observed and the increase did not reach statistical significance). As a result, the panel recommended a Group D chemical classification (Not Classifiable as to Human Carcinogenicity) for glyphosate and advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify the unresolved questions (FIFRA SAP Report, 1986)[3].

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[1] Additional information on the Registration Review process can be found at: https://www.epa.gov/pesticide-reevaluation/registration-review-process

[2] Documents of the Registration Review can be found in the public docket at: EPA-HQ-OPP-2009-0361, accessible at www.regulations.gov.

[3] Review available at: http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

With the submission of two rat carcinogenicity studies following this data call-in, a second peer review was conducted in 1991 by the agency's Carcinogenicity Peer Review Committee (CPRC) to incorporate the new data. In accordance with the agency's 1986 Draft Guidelines for Carcinogen Risk Assessment, the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Most recently, in September 2015, a third review was done by the Cancer Assessment Review Committee (CARC). Relevant glyphosate data available to EPA at that time for glyphosate were reevaluated, including studies submitted by the registrant and studies published in the open literature. The agency performed this evaluation in support of Registration Review in accordance with the 2005 Guidelines for Carcinogen Risk Assessment, classified glyphosate as "Not Likely to be Carcinogenic to Humans" (CARC, 2015; TXR #0057299).

In recent years, several international agencies have evaluated the carcinogenic potential of glyphosate. In March 2015, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), determined that glyphosate was a probable carcinogen (group 2A) (IARC, 2015). Later, in November 2015, the European Food Safety Authority (EFSA) determined that glyphosate was unlikely to pose a carcinogenic hazard to humans (EFSA, 2015). In May 2016, the Joint Food and Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR), another subdivision of the WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet (JMPR, 2016). Some individual countries in Europe (e.g., France, Sweden) have considered banning glyphosate uses based on the IARC decision, while other countries (e.g., Japan, Canada, Australia, New Zealand) have continued to support their conclusion that glyphosate is unlikely to pose a carcinogenic risk to humans.

The recent peer review performed by CARC served as an initial analysis to update the data evaluation for glyphosate at that time. Based on an evaluation of the studies included in the recent analyses by IARC, JMPR, and EFSA, the agency then became aware of additional relevant studies not available to EPA. As a result, EPA also requested information from registrants about studies that existed, but had never been submitted to the agency. The current evaluation incorporates these additional studies. In addition, the agency conducted a systematic review of the open literature and toxicological databases for glyphosate by using a "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment". As such, the current evaluation also provides a more thorough evaluation than the 2015 CARC review.

In December 2016, the FIFRA SAP was convened to evaluate the agency's Issue Paper regarding the human carcinogenic potential of glyphosate. The panel's report was published in March 2017 and the current document incorporates revisions based on the panel's report (G. Akerman; 12-DEC-2017; TXR#0057689). Additionally, information from a recently published analysis of glyphosate use and cancer incidence in the Agricultural Health Study (AHS) cohort (Andreotti et al., 2017) with a longer follow-up than the previously published data (De Roos et al., 2005) has been considered in this evaluation.

1.3 Overview of "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment"

In 2010, the Office of Pesticide Programs (OPP) developed a draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" which provides the foundation for evaluating multiple lines of scientific evidence in the context of understanding of the mode of action (MOA)/adverse outcome pathway (AOP) (U.S. EPA, 2010). The draft framework, which includes two key components, problem formulation and use of the MOA/AOP pathway frameworks, was reviewed favorably by the FIFRA SAP in 2010 (FIFRA SAP, 2010). In 2016, a final version of the framework was published[4], which incorporated improvements based on recommendations from the SAP, public comments, and the experience gained since 2010 conducting assessments on several pesticides for which epidemiological data were available. Recently, EPA has applied this framework to the evaluation of atrazine and chlorpyrifos[5].

OPP's framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety MOA/human relevance framework, which highlights the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek *et al.*, 2014). Consistent with recommendations by the National Research Council (NRC) in its 2009 report on *Science and Decisions*, OPP's framework describes the importance of using problem formulation at the beginning of a complex scientific analysis. The problem formulation stage starts with planning dialogue with risk managers to identify goals for the analysis and possible risk management strategies. This initial dialogue provides the regulatory context for the scientific analysis and helps define the scope of such an analysis. The problem formulation stage also involves consideration of the available information regarding the pesticide use/usage, toxicological effects of concern, and exposure pathways and duration along with key gaps in data or scientific information. Specific to glyphosate, the scoping document prepared for Registration Review (J. Langsdale *et al.*, 2009) along with the review conducted by the CARC (CARC, 2015) represent the problem formulation analyses for the weight-of-evidence evaluation for carcinogenic potential. A summary of the US exposure profile is provided in Section 1.4 to provide context for interpreting the various lines of evidence.

One of the key components of the agency's framework is the use of the MOA framework/AOP concept (Figure 1.1) as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies. Specifically, the modified Bradford Hill Criteria (Hill, 1965) are used to evaluate strength, consistency, dose response, temporal concordance and biological plausibility of multiple lines of evidence in a weight-of-evidence analysis.

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[4] https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

[5] Chlorpyrifos Revised Human Health Risk Assessment for Registration Review; 29-DEC-2014; D424485.
U.S. EPA 2010 SAP Background White Paper – Re-evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. EPA-HQ-OPP-2010-0125.
U.S. EPA 2011 SAP Issue Paper – Re-evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. EPA-HQ-OPP-2011-0399.

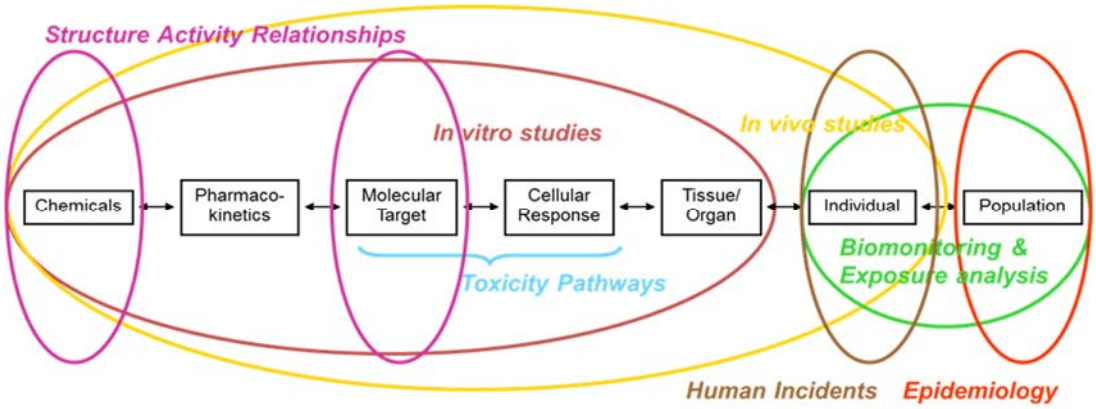

Figure 1.1. Source to outcome pathway (adapted from NRC, 2007).

1.4 Summary of the Exposure Profile in the United States

All pesticide products provide critical information about how to safely and legally handle and use pesticide products. Pesticide labels are legally enforceable and all carry the statement "it is a violation of Federal law to use this product in a manner inconsistent with its labeling." In other words, the label is law. As a result, a key function of the pesticide product label is to manage the potential risk from pesticides.

Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. It is also registered for use on glyphosate-resistant (transgenic) crop varieties such as corn, soybean, canola, cotton, sugar beets, and wheat. Registered tolerances in the United States include residues of the parent compound glyphosate and *N*-acetyl-glyphosate, a metabolite found in/on glyphosate-tolerant crops[6].

Dietary (food and water) exposures are anticipated from applications to crops. Since there are registered uses of glyphosate that may be used in residential settings, residential handlers may be exposed to glyphosate during applications. Exposures may also occur from entering non-occupational areas that have been previously treated with glyphosate. Occupational/commercial workers may be exposed to glyphosate while handling the pesticide prior to application (mixing and/or loading), during application, or when entering treated sites. The agency considers all of the anticipated exposure pathways as part of their evaluation for human health.

Oral exposure is considered the primary route of concern for glyphosate. Oral absorption has been shown to be relatively low for glyphosate (~30% of administered doses) with negligible accumulation in tissues and rapid excretion (primarily unchanged parent) via the urine. Due to its low vapor pressure, inhalation exposure to glyphosate is expected to be minimal. Dermal penetration has also been shown to be relatively low for human skin (<1%) indicating dermal exposure will only contribute slightly to a systemic biological dose. Furthermore, in route-

[6] All currently registered tolerances for residues of glyphosate can be found in the Code of Federal Regulations (40 CFR §180.364).

specific inhalation and dermal toxicity studies, no adverse effects were observed. This all suggests that there is low potential for a sustainable biological dose following glyphosate exposure.

In residential/non-occupational settings, children 1-2 years old are considered the most highly exposed subpopulation with oral exposures from dietary (food and water) ingestion and incidental oral ingestion (e.g., hand-to-mouth activities) in treated areas. There is also potential for dermal exposures in previously treated areas. Using OPP's standard exposure assessment methodologies which are based on peer-reviewed and validated exposure data and models[7], a high-end estimate of combined exposure for children 1-2 years old is 0.47 mg/kg/day (see Appendix E).

At the time of initial registration (1974), total use of glyphosate in the United States was approximately 1.4 million pounds (Benbrook, 2016). In 1995, total use of glyphosate increased to approximately 40 million pounds with agriculture accounting for 70% of use. With the introduction of transgenic crop varieties in the United States circa 1996, (such as soybean, cotton, and corn) use of glyphosate increased dramatically (Green and Owen, 2011), and in 2000 the total use of glyphosate in the United States was approximately 98.5 million pounds. By 2014, total annual use of glyphosate was approximately 280-290 million pounds (based on Benbrook, 2016 and industry proprietary data accessible to EPA) with agriculture accounting for 90% of use. Although glyphosate use has continuously increased up to 2012, the stabilization of glyphosate usage in recent years is due to the increase in a number of glyphosate-resistant weed species, starting with rigid ryegrass identified in California in 1998 and currently totaling 16 different weed species in the United States as of March 2016. Figure 1.2 below provides a visual representation of the increased agricultural use of glyphosate in the United States using proprietary market research data from 1987-2014.

The increased use of glyphosate may be partly attributed to an increase in the number of farmers using glyphosate; however, it is more likely that individuals already using glyphosate increased their use and subsequent exposure. With the introduction of transgenic crop varieties, glyphosate use shifted from pre-emergent to a combination of pre- and post-emergent applications. Additionally, application rates increased in some instances and more applications were allowed per year (2-3 times/year). Maps from the United States Geological Survey (USGS) displaying glyphosate use in the United States indicate that although use has drastically increased since 1994, areas treated with glyphosate for agricultural purposes appear to be approximately the same over time (Figures 1.3-1.4). The introduction of transgenic crops in some cases led to a shift in crops grown on individual farms, such that more acreage within the farm would be dedicated to growing the glyphosate-tolerant crops replacing other crops. In addition, during the 2000s there was also an increase in growing corn for ethanol production, which could also have resulted in increased acreage dedicated glyphosate-tolerant corn.

[7] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

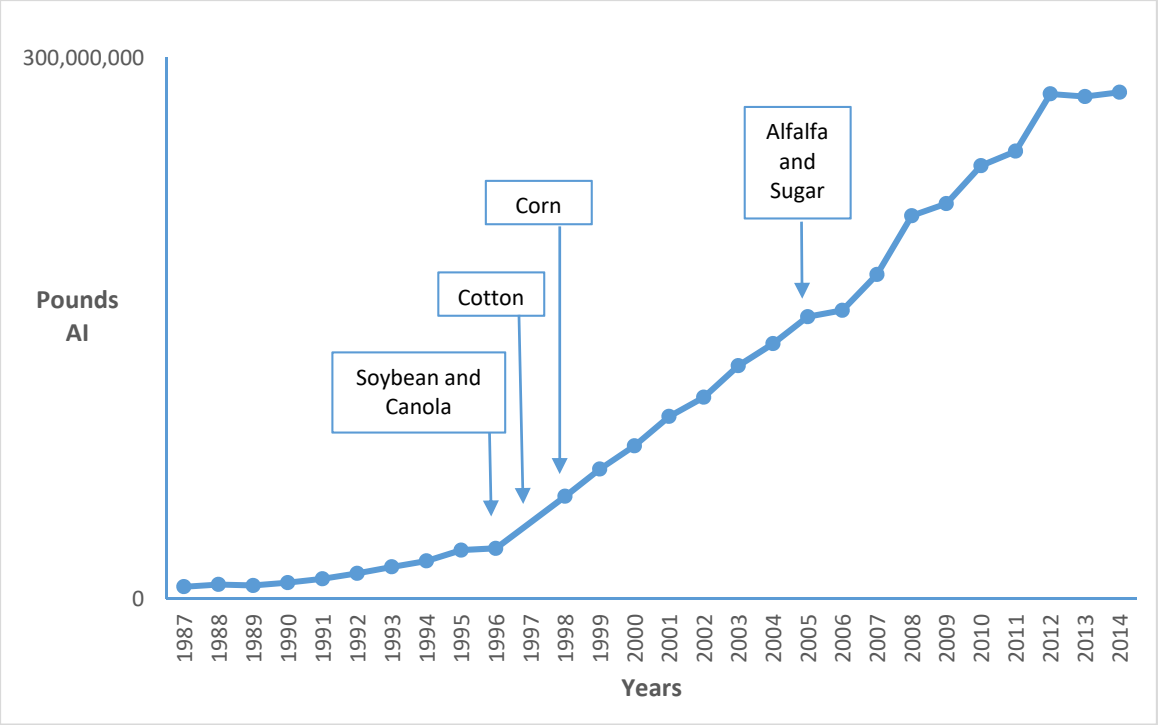

Figure 1.2. Glyphosate agricultural usage (pounds applied annually) from 1987- 2014. Boxes indicate years when glyphosate-resistant crops were introduced. Source: Proprietary Market Research Data (1987 – 2014).

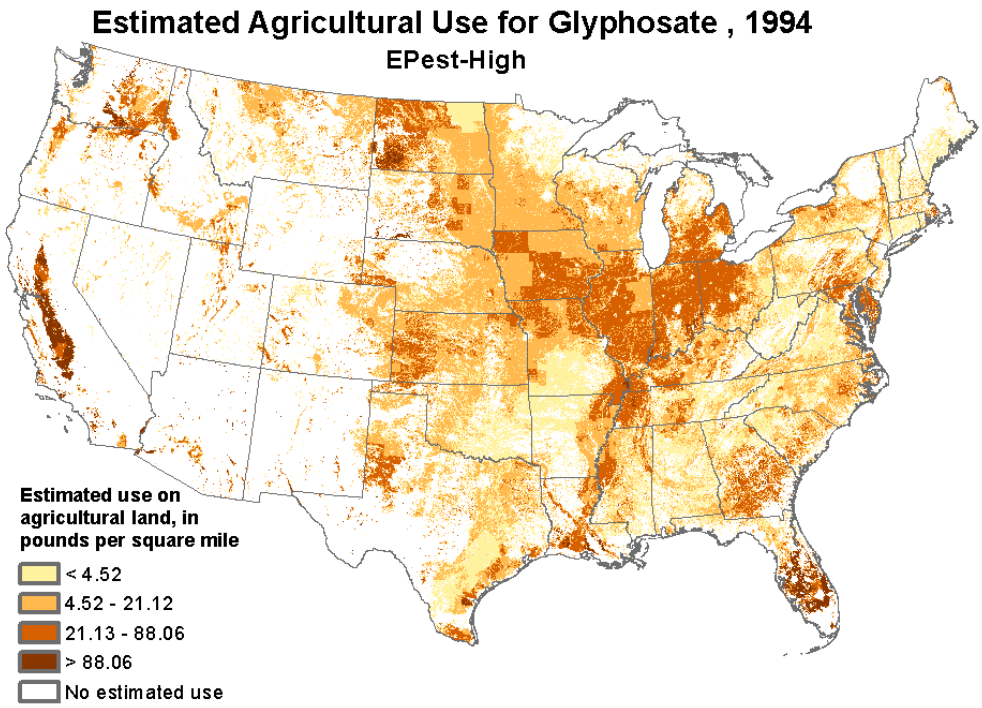

Figure 1.3. Map of estimated agricultural use for glyphosate in 1994 from USGS (http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=1994&map=GLYPHOSATE&hilo=H)

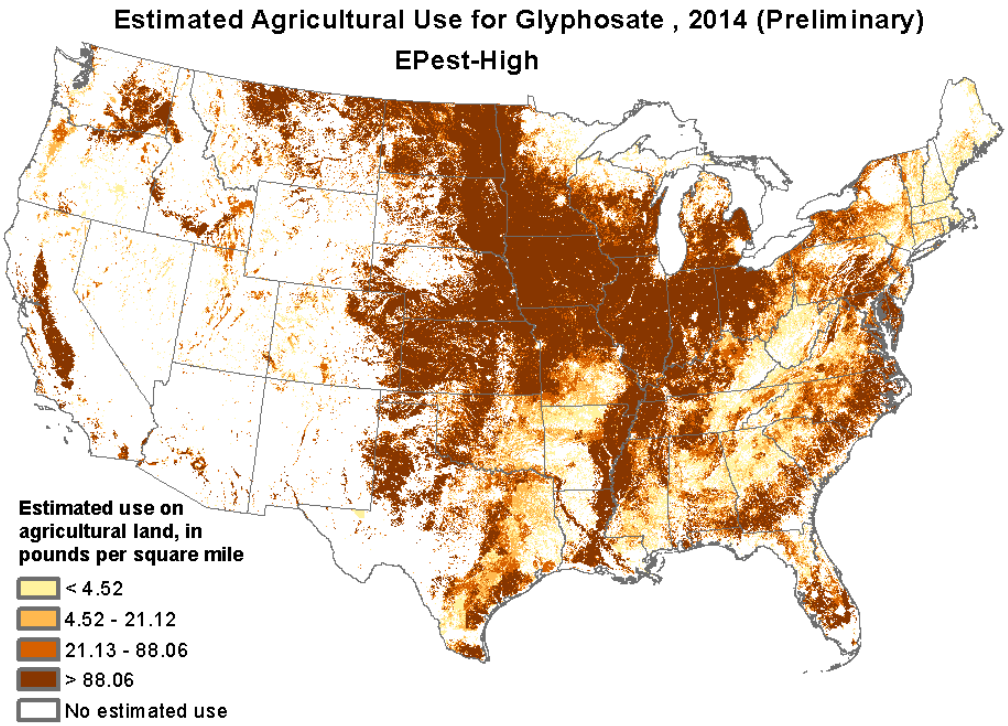

Figure 1.4. Map of estimated agricultural use for glyphosate in 2014 from USGS (http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2014&map=GLYPHOSATE&hilo=H)

The potential exposure to occupational handlers is dependent on the formulation, specific task (mixer, loader, and/or applicator), rate of application, and acreage treated. Using HED's standard occupational exposure assessment methodologies which are based on peer-reviewed and validated exposure data and models[8], mixer/loaders result in the highest potential exposure estimates. Assuming no personal protective equipment (PPE), exposure estimates for mixer/loaders range from 0.03-7 mg/kg/day using the maximum application rate for high acreage agricultural crops (6 lb ai/acre)[9]. For applicators, exposure would be lower with estimates ranging from 0.02-0.03 mg/kg/day using the same application rate and acreage.

The maximum potential exposures from currently registered uses of glyphosate in residential and occupational settings in the United States are used in the current evaluation to aid in the determination of whether findings in laboratory studies are relevant for human health risk assessment. In Sections 4.0 and 5.0, descriptions are provided for animal carcinogenicity and genotoxicity studies, respectively. Results from these studies, particularly those administering high doses, are put into context with the human exposure potential in the United States.

[8] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

[9] Based on use information provided by the Joint Glyphosate Task Force for the following end-use products: EPA Registration Nos.: 100-1182, 228-713, 524-343, 524-475, 524-537, 524-549, 524-579, 4787-23, and 62719-556.

1.5 Organization of this Document

In this analysis of the human carcinogenic potential of the active ingredient glyphosate, the agency has performed a comprehensive analysis of available data from submitted guideline studies and the open literature. This includes epidemiological, animal carcinogenicity, and genotoxicity studies. Consistent with the framework described in Section 1.3, the agency has evaluated these multiple lines of evidence and conducted a weight-of-evidence analysis. Although there are studies available on glyphosate-based pesticide formulations, the agency is soliciting advice from the FIFRA SAP on this evaluation of human carcinogenic potential for the active ingredient glyphosate only at this time. The remainder of this document is organized by the following:

- *Section 2.0 Systematic Review & Data Collection Methods* provides a description of methods used to compile all relevant studies used in the current evaluation.
- *Section 3.0 Data Evaluation of Epidemiology* describes the available epidemiological studies, evaluates relevant studies for study quality, and discusses reported effect estimates.
- *Section 4.0 Data Evaluation of Animal Carcinogenicity Studies* provides a description and evaluation of the available animal carcinogenicity studies for glyphosate.
- *Section 5.0 Data Evaluation of Genetic Toxicity* summarizes and discusses the various genotoxicity assays that have been tested with glyphosate.
- *Section 6.0 Data Integration & Weight of Evidence Analysis Across Multiple Lines of Evidence* integrates available data discussed in Sections 3.0-5.0 to consider concepts, such as strength, consistency, dose response, temporal concordance and biological plausibility in a weight-of-evidence analysis. This section also provides discussion of the data in the context of cancer descriptors provided in the 2005 Guidelines for Carcinogen Risk Assessment.
- *Section 7.0 Collaborative Research Plan for Glyphosate and Glyphosate Formulations* provides a discussion of planned research that is intended to evaluate the role of glyphosate in product formulations and the differences in formulation toxicity.

2.0 Systematic Review & Data Collection

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 (NRC, 2011). 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" (NRC, 2014). Consistent with NRC's recommendations, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures. In short, OCSPP employs "fit for purpose" systematic reviews that rely on standard methods for ***collecting, evaluating, and integrating*** the scientific data supporting the agency's decisions. The concept of fit for purpose implies that a particular activity or method is suitable for its intended use. Inherent in this definition is the concept that one size does not fit all

situations and thus flexibility is allowed. However, it is notable that with flexibility comes the importance of transparency of documented processes; including the importance of transparency and clarity in approaches to data collection, evaluation, and integration. These are described throughout the document with data collection in Sections 2.1.1-2.1.2, evaluation in Sections 3-5, and integration in Section 6.

As a result, more recent evaluations are starting to reflect this progression in the agency's process. Similar to the framework for incorporating human epidemiologic and incident data, systematic review begins with a problem formulation to determine the scope and purpose of the search. Studies are considered based on their relevance to answer specific questions and those studies deemed relevant are then further considered for their usefulness in risk assessment.

The agency strives to use high-quality studies when evaluating the hazard potential of pesticidal chemicals and considers a broad set of data during this process. This includes registrant generated studies required under FIFRA, as well as peer-reviewed scientific journals and other sources, such as other governments and academia. 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. In this way, hazards are identified and potential risks characterized to ensure that decisions are informed by the best science available.

2.1 Data Collection: Methods & Sources

Data were collected by searching the open literature (Section 2.1.1) and other publicly available sources (e.g., recent internal reviews, evaluations by other organizations) (Section 2.1.2). Internal databases were also searched for submitted studies conducted according to Organization for Economic Cooperation and Development (OECD) test guidelines, OCSPP harmonized test guidelines, and other pesticide test guidelines (OPP guidelines) (Section 2.1.2).

It should be noted that glyphosate is primarily manufactured as various salts with cations, such as isopropylamine, ammonium, or sodium. These salts are derivatives of the active substance glyphosate and increase the solubility of technical-grade glyphosate acid in water. All of these forms were considered for the current evaluation.

2.1.1 Open Literature Search

As part of the evaluation of the human carcinogenic potential of glyphosate, the literature review described here uses concepts consistent with fit for purpose systematic review, such as detailed tracking of search terms and which literature have been included or excluded. The primary goal of the literature search was to identify relevant and appropriate open literature studies that had the potential to inform the agency on the <u>human</u> carcinogenic potential of glyphosate. Therefore, non-mammalian studies were not considered, and several terms were used in the search string in an attempt to exclude non-mammalian studies.

To obtain literature studies, OPP worked with EPA librarians to conduct searches in PubMed, Web of Science, and Science Direct. A search was conducted on May 6, 2016 in PubMed and Web of Science using the following search string to yield 141 and 225 results, respectively:

> ((glyphosate OR "1071-83-6" OR roundup OR "N-(Phosphonomethyl)glycine") AND (aneuploid* OR chromosom* OR clastogenic* OR "DNA damag*" OR "DNA adduct*" OR genome* OR genotoxic* OR micronucle* OR cancer* OR carcinogen* OR oncogenic* OR mutagen* OR cytotoxic* OR tumor* OR tumour* OR malignanc* OR neoplasm* OR *oma)) NOT (fish* OR frog* OR tadpole* OR insect* OR eco* OR amphibian* OR reptil* OR invertebrate* OR fly OR flies OR aquatic OR bird* OR aqueous OR water OR yeast* OR worm* OR earthworm* OR bacteria* OR lichen OR resist* OR "herbicide resist")

Due to differences with using Science Direct, the search string was slightly changed. This search was also conducted on May 6, 2016 and yielded 459 results:

> ((glyphosate OR "1071-83-6" OR roundup OR "N-(Phosphonomethyl)glycine") AND (aneuploid* OR chromosom* OR clastogenic* OR (DNA pre/2 (damag* OR adduct*)) OR genome* OR genotoxic* OR micronucle* OR cancer* OR carcinogen* OR oncogenic* OR mutagen* OR cytotoxic* OR tumor* OR tumour* OR malignanc* OR neoplasm* OR *oma)) AND NOT (eco* OR fish* OR frog* OR tadpole* OR invertebrate* OR bird* OR insect* OR fly OR flies OR amphibian* OR reptil* OR yeast* OR aquatic OR aqueous OR water OR worm* OR earthworm* OR bacteria* OR lichen OR resist* OR "herbicide resist”)

After cross-referencing the results obtained from the three open literature searches for duplicates, a total of 735 individual articles were obtained (Appendix A) and one additional study (Alvarez-Moya et al., 2014) not identified in the search was added to this list for a total of 736 individual articles. Three staff members independently evaluated all of the studies and came to consensus on which studies would be considered relevant to the issue of concern (i.e., human carcinogenic potential of glyphosate). Many of the articles were not considered to be within the scope of the search or not considered relevant in general (657 articles). Additionally, 27 articles were not appropriate due to the type of article (i.e., correspondence, abstract only, not available in English, retraction). Of the 52 relevant articles, 42 were used in the current evaluation (31 genotoxicity, 9 epidemiological, and 2 animal carcinogenicity). Three articles also reported on the potential of glyphosate and its metabolites to be developed into therapeutic drugs for cancer treatment. The remaining 7 articles evaluated effects on glyphosate or glyphosate formulations on cellular processes, mostly focusing on epidermal cells, and were not considered informative for the current evaluation.

2.1.2 Studies Submitted to the Agency

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 OECD, OCSPP, or OPP accepted protocols and guidelines, which ease comparisons across studies and chemicals.

The toxicological databases for glyphosate[10] were reviewed and all relevant animal, genotoxicity, and metabolism studies were collected for consideration.

Several resources were used to ensure all relevant studies were included in the current evaluation. The list of studies obtained from the toxicological database and the open literature search were cross-referenced with recent internal reviews (CARC, 2015; S. Recore *et al.*, 2014). This list was also cross-referenced with review articles from the open literature [Chang and Delzell (2016), Greim et al. (2015), Kier and Kirkland (2013), Kier (2015), Mink *et al.* (2012), Schinasi and Leon (2014), and Williams *et al.* (2000)][11]. EPA requested studies from registrants that were not previously available to the EPA. As a result, numerous studies were subsequently submitted to the agency. Study reports for one animal carcinogenicity study and 17 genotoxicity studies were not available to the agency and have been noted in the relevant sections below. For these studies, data and study summaries provided in Greim et al. (2015) and Kier and Kirkland (2013) were relied upon for the current evaluation.

2.2 Evaluation of Relevant Studies

Studies submitted to the agency are evaluating based on OECD, OCSPP, or OPP test guideline requirements to determine whether studies are acceptable for use in risk assessment. In the current evaluation, animal carcinogenicity, genotoxicity, and metabolism studies located in the internal databases with access to full study reports were evaluated in this manner. Those classified as unacceptable were noted and subsequently excluded from the current evaluation.

In order to evaluate open literature studies, criteria described in the OPP guidance for considering and using open literature toxicity studies to support human health risk assessment was utilized (U.S. EPA, 2012). 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. As with submitted studies, those deemed unacceptable were noted and subsequently excluded from the current evaluation.

[10] Glyphosate pesticide chemical (PC) codes: 103601, 103603, 103604, 103605, 103607, 103608, 103613, 128501, and 417300.

[11] All review articles, except Schinasi and Leon (2014), were funded and/or linked to Monsanto Co. or other registrants.

3.0 Data Evaluation of Epidemiology

3.1 Introduction

Epidemiological studies are valuable for risk assessment since they may provide direct evidence on whether human exposure to a chemical may cause cancer. Studies of high quality and adequate statistical power are preferable and remove the need to account for extrapolation from animals to humans or extrapolation from high to low doses. Epidemiological studies can also be integrated with experimental evidence when determining or clarifying the carcinogenic potential of a chemical for risk assessment. The key considerations in evaluating epidemiologic studies are study design, exposure assessment, outcome assessment, confounding control, statistical analyses, and risk of other bias.

OPP routinely evaluates the available epidemiological literature. As part of Registration Review of glyphosate, an evaluation was initially conducted in 2014 (S. Recore *et al.*, 2014) and subsequently another evaluation was performed in 2015 (CARC, 2015). The 2015 evaluation began with the epidemiological studies previously identified in the 2014 evaluation and included three additional studies that were not included in the 2014 evaluation. These studies were identified in review articles, included in the evaluation by IARC (2015), or were published since the 2014 OPP evaluation. Both the 2014 and 2015 OPP evaluations considered the design and overall quality of the epidemiological studies; however, formal study quality evaluations and rankings were not conducted. In the current review, all of the studies in the 2015 report, as well as additional epidemiological articles identified from a comprehensive search and cross-referencing with available resources as described under Section 2.0, were considered in the current evaluation. The following sections provide a description of how epidemiological studies were evaluated for study quality and subsequent overall rankings, a summary of relevant studies, and a discussion of the overall results.

3.2 Considerations for Study Quality Evaluation and Scope of Assessment

This section summarizes how specific study characteristics were factored into the determination of a study's overall quality category. It should be noted that these study quality considerations are specific to the issue of concern (i.e., carcinogenic potential of glyphosate). These considerations are considered 'fit-for-purpose' under this context and could differ in another regulatory or scientific context. Although the basic concepts apply broadly, the study quality considerations are tailored specifically to studies investigating the association between glyphosate exposure and cancer outcomes. As with all research studies, the design elements of an epidemiological study have potential impacts on study quality and relevance to the research question under investigation. Each study was, therefore, judged to be of high, moderate, or low quality in each of the following six domains affecting study quality: study design, exposure assessment, outcome assessment, confounder control, statistical analysis, and susceptibility to bias (See Section 3.2.1 and Table 3.1 for general considerations under each domain). A similar approach was recently used by OPP for the evaluation of epidemiological studies for organophosphate pesticides (A. Lowit *et al.,* 2015).

Primary literature and associated meta-analyses evaluating the association between glyphosate exposure and a cancer outcome were the focus of this analysis. Reviews were only used to identify individual studies that should be considered for study evaluation. Commentaries, correspondence, and letters to the editor without original data were excluded. Of the relevant studies identified, studies with the most complete analyses utilizing the greatest number of cases and controls (e.g., pooled case-control studies) were evaluated for ranking (see Appendix B for visual representation of these studies). If studies did not collect exposure information on glyphosate from individual subjects, did not assess an outcome (e.g., biomonitoring studies), and/or did not provide a quantitative measure of an association between glyphosate and a cancer outcome, then these studies were assigned a low quality ranking and were not further evaluated in detail (see Figure 3.1). A similar process was used by JMPR for their identification of epidemiological studies for evaluating the carcinogenic potential of glyphosate and two other pesticides (JMPR, 2016).

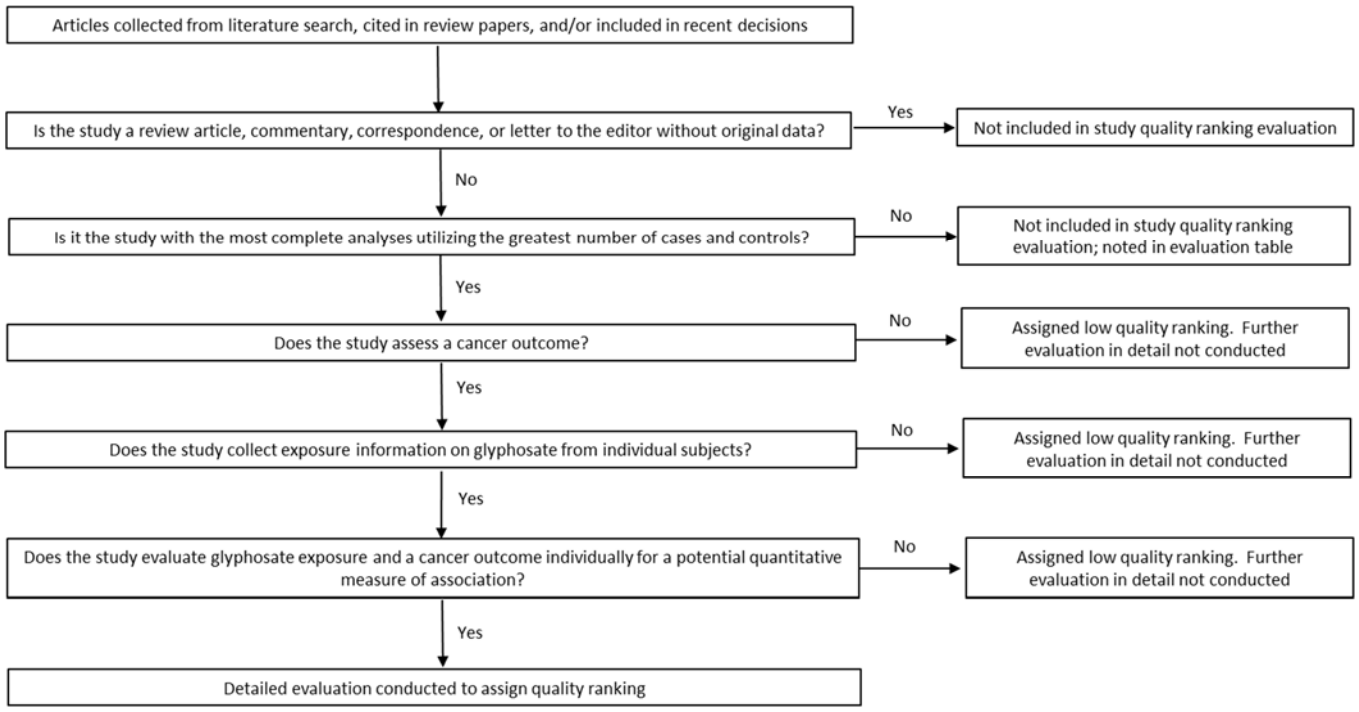

Figure 3.1. Study evaluation process for epidemiological studies.

3.2.1 Study Designs

In judging an individual study's contribution to the strength of evidence in the epidemiologic literature base, the following general hierarchy of observational study designs was considered (from most to least preferred): prospective cohort study (including nested case-control studies), case-control study, and cross-sectional study. It is important to note, however, that this hierarchy of study designs reflects the *potential* for the collection of high quality information (related to exposure, outcome, confounders, and effect modifiers) and *potential* for efficient and valid estimation of the true association. Thus, in deliberating on quality, care has been taken to

consider the circumstances and particulars of each individual study to consider whether the study was well conducted independent of the type of study design.

The study designs used in the epidemiological literature reviewed were analytical and descriptive studies. Cohort and case-control study designs are analytical studies used to evaluate relative incidence of health and disease outcomes by exposure status. Cross-sectional and ecological studies are generally considered descriptive or hypothesis-generating study designs; however, they can also be used to test hypotheses regarding prevalence of health outcomes and, under certain conditions, incidence as well.

Table 3.1. Epidemiological Study Quality Considerations[a].

Parameter	High Score	Moderate Score	Low Score
Study Design	Cohort	Case-control	Cross-sectional/Ecological
Exposure Assessment	Questionnaire and/or interview answered by subjects for chemical-specific exposure	Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use of pesticides in general evaluated
Outcome Assessment	State or National registries, physicians, and/or special surveillance programs with cases verified by histopathological evaluation for tumors; appropriate consideration of prevalent vs. incident cases; analysis by valid method specific for biomarkers	State or National registries, physicians, and/or special surveillance programs without histopathological verification for tumors; analysis by assays that are less specific for biomarkers of interest	No outcome evaluated; unclear/no consideration for whether prevalent or incident cases are appropriate; biomarker methods not validated
Confounder Control	Good control for important confounders related to cancer, standard confounders, and known confounders for glyphosate and cancer outcomes (e.g., exposure to multiple pesticides) through study design or analytic control with well measured co-exposures (i.e., cumulative exposure)	Moderately good control for confounders related to cancer; standard variables accounted for and; attempt to control for known confounders via a less efficient measure of co-exposure (e.g., ever/never use)	No adjustments for confounders
Statistical Analyses	Appropriate to study question and design, supported by relatively adequate sample size, maximal use of data, reported well	Acceptable methods, lower/questionable study power or sample size	Minimal attention to statistical analyses, sample size evidently low, comparison not performed or described clearly

Table 3.1. Epidemiological Study Quality Considerations[a].			
Parameter	**High Score**	**Moderate Score**	**Low Score**
Risk of (Other) Bias	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of effect estimate, no/low potential of selection bias	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate, evidence of potential selection bias with low impact on effect estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanation for study findings, evidence of selection bias with high potential to impact effect estimate

[a] Overall study quality ranking based on comprehensive assessment across the parameters.

3.2.1.1 Analytical Studies

(1) Cohort Study

In a typical cohort study, such as the AHS, individuals are classified according to exposure status (i.e., presence, absence, or magnitude of exposure) and then followed over time to quantify and compare the development (i.e., incidence) of the health outcome of interest by exposure group. Conceptually, the non-exposed comparison group in a cohort study provides an estimate of the incidence of the outcome among the exposed, had they, counter-to-fact, not been exposed. Apart from chance variations, a valid cohort study comparing exposed individuals to non-exposed individuals provides an estimate of the relative risk (or rate) of the disease associated with exposure. Ideally, the exposed and non-exposed groups are exchangeable, in the sense that switching the exposed to non-exposed, and non-exposed to exposed would yield the same measure of association (e.g., relative risk). If this were the case then, apart from chance, a cohort study would yield a measure of association equivalent to that produced in a corresponding (intervention) study where exposure status was randomly assigned.

The chief advantage of the cohort study design is that it affords the investigator the opportunity to avoid and/or adjust for potential biases (i.e., selection bias, information bias, and confounding); however, these biases may also be avoided in other well-designed study designs, such as a case-control study. Cohort studies also allow for discernment of the chronological relationship between exposure and outcome, and can be particularly efficient for studying uncommon exposures. The primary disadvantage of the cohort study design is logistical inefficiency with respect to the necessary time, expense, and other resources needed to conduct them. Cohort studies are particularly inefficient for evaluating associations with rare outcomes and diseases with long induction or latency periods. Case-control studies that are nested within a cohort study (nested case-control studies) share the attributes of the cohort study and may be more efficient. However, when follow-up throughout the study period is incomplete, the potential for selection bias is increased, especially if follow-up rates are related to exposure status.

Two sub-categories of cohort studies – prospective and retrospective – are often applied to distinguish between studies in which the health outcome has occurred (retrospective study), or has not occurred (prospective study) at the time the investigators initiate the study. This distinction is important primarily as it pertains to the potential differences in the quality (e.g.,

completeness, accuracy, and precision) of information that can be ascertained by the investigators, and also as it relates to potential sources of bias. Although not always true, the prospective study design is considered the preferable of the two, as investigators can potentially have more choices in determining how exposure, outcome, and covariate information is collected. In a retrospective study conducted to evaluate the same hypothesis, by contrast, the investigators would have to rely on exposure information based on self-reporting or historical records. Such reporting is subject to (human) errors in recall, however when such errors are uncorrelated with disease state, there can be a bias towards the null due to random exposure measurement error (information bias) and only when such errors are correlated with the disease state can there be bias away from the null.

(2) Case-Control Study

In a typical case-control study, individuals are classified according to their outcome status (i.e., cases who have developed the outcome of interest, and controls who represent the population from which the cases arise). The relative odds of exposure are then compared between cases and controls. The primary advantage of case-control studies is that they are logistically efficient relative to cohort studies, often being conducted at a fraction of the cost and in a fraction of the time as a corresponding cohort study. Case-control studies can be used to examine associations between multiple exposures and a given health outcome. They are particularly efficient for evaluating rare outcomes, but are inefficient for studying uncommon exposures. An important point to evaluate in each case-control study is the potential for selection bias, which arises if the exposure distribution among the control subjects is not representative of the exposure distribution among the population that gave rise to the cases. When participation rates between cases and controls are low or distinctly imbalanced, the potential for selection bias is increased, especially if participation rates are related to exposure status. Case-control studies that rely on self-reported exposure measures are also potentially susceptible to information bias which could result in bias towards the null or away from the null.

3.2.1.2 Descriptive Studies

Cross-sectional studies are used to evaluate associations between exposure and outcome prevalence in a population at a single point in (or period of) time. The primary advantage of a cross-sectional study is logistical efficiency. They are relatively quick and inexpensive to conduct, as a long period of follow-up is not required, and exposure and outcome assessments occur simultaneously. Cross-sectional studies have three primary *potential* disadvantages: 1) potential difficulty in discerning the temporal relationships (i.e., whether the exposure precedes the outcome); 2) estimating outcome prevalence rather than incidence of the outcome; and 3) the possible overrepresentation of cases of the outcome with long duration relative to the average in the population, and often with a better prognosis.

Ecological studies are used to evaluate associations between exposures and outcomes using population-level rather than individual-level data. The primary advantages of ecological studies are related to logistical efficiency, as they often rely on pre-existing data sources and require no individual-level exposure, outcome, or covariate assessments. The primary weakness of the ecologic study is the potential for confounding and resultant inappropriate extrapolation of associations observed on the aggregate-level to associations on an individual level. The

discrepancy that associations observed at the population level are not observed at the individual level is referred to as the ecological fallacy. Semi-ecological studies are less susceptible to the ecological fallacy due to incorporation of individual-level data on outcomes and/or confounders. The quality of these studies depends on the ability of the group exposure data to represent individual exposure and the research question of interest.

3.2.2 Exposure Measures

As described in Section 3.2 and Figure 3.1, studies assigned a low quality ranking based on an initial evaluation were not further evaluated in detail. In all of the studies included in the analysis that were reviewed and ranked for study quality, exposure information was collected from subjects and/or proxy individuals via questionnaires and/or interviews. These exposure assessments typically include questions to determine the amount of direct pesticide use or to collect information on behaviors and conditions associated with pesticide use (e.g., occupation, tasks). This type of reporting likely misclassifies actual pesticide exposure. If conducted as part of a prospective exposure assessment, these errors are likely to be non-differential with respect to the outcome(s) of interest. In a retrospective assessment, the subject or proxy has knowledge of the outcome; therefore, these errors may be differential or non-differential. Studies that exclusively used subjects rather than including proxy individuals were considered more reliable and given a higher weight given that the subjects would have a more accurate recollection of their own exposure.

3.2.3 Outcome Measures

All of the studies evaluated in detail, except one, utilized state or national cancer registries, physicians, and/or special surveillance programs to determine outcome status (i.e., subjects with or without a cancer of interest). In several studies, the cases were also verified by histopathological evaluation. Overall, outcome measures were relatively consistent across studies and these assessments are likely to have minimal errors. The remaining study evaluated in detail (Koureas et al., 2014) assessed oxidative DNA damage rather than a type of cancer. For this evaluation, the oxidation by-product 8-hydroxydeoxyguanosine (8-OHdG) was measured by enzyme immunoassay. This type of assay generally exhibits low specificity. More sensitive quantitative methods are available to analyze genomic DNA for 8-OHdG by high-performance liquid chromatography (HPLC) with electrochemical detection, gas chromatography-mass spectrometry (GC-MS), and HPLC tandem mass spectrometry. Consideration of incident or prevalent cases should also be carried out. By using only incident cases, there is greater confidence that exposures occurred prior to the development of the outcomes. Inclusion of prevalent cases can lead to an over-representation of cases with a long course of disease.

3.2.4 Confounding

The degree to which confounders were controlled varied across studies. Some studies adjusted for particular medical variables, while others did not. Some standard variables, such as age, geographical location, and sex, were either adjusted for analytically or by matching in case-control studies. Several studies collected information on potential confounders; however, not all of these variables were evaluated or results of the evaluation were not reported. The direction and magnitude for confounders are, in general, difficult to determine because they are dependent

upon the relationship of each confounding factor with glyphosate and the cancer under investigation. Several studies considered the potential for confounding from co-exposure to other pesticides; however, only a few reported effect estimates between glyphosate exposure and cancer risk adjusted for the use of other pesticides. Given most people in the epidemiological studies who use pesticides occupationally will be exposed to multiple pesticides and, in some instances, those other pesticides were observed to be risk factors for the same cancer, this is a particularly important concern to address in either the study design or in the statistical analyses. Across numerous studies, co-exposures to other pesticides was found to be positively correlated with exposure to glyphosate and exposure to those other pesticides appear to increase the risk of some cancers. As a result, the direction of confounding would be to inflate any true effect of glyphosate in the absence of statistical control. This underlines the importance of adjusting for co-exposures to other pesticides.

For NHL, other potential confounders, such as exposure to diesel exhaust fumes, solvents, ultraviolet radiation, livestock, and viruses, have been identified. Some of these are more plausible than others. For example, occupational exposure to diesel exhaust fumes (e.g., McDuffie et al., 2002; Karunanayake et al. 2008; Baris et al. 2001; Maizlish et al. 1998) and solvents (Wang et al., 2009; Kato et al., 2005; Olsson and Brandt, 1988) are considered likely to increase the risk of NHL. Agricultural workers are exposed to diesel fumes when using agricultural vehicles when applying pesticides, such as glyphosate, and when using heavy equipment during mixing, loading, and/or applying pesticides. Agricultural workers are also exposed to solvents. Solvents are often used in pesticide products to aid the delivery of the active ingredient and enhance efficacy. Solvents are also used for cleaning and maintenance/repair of agricultural equipment used for mixing, loading, and/or applying pesticides. With an association between exposure and outcome of interest, it is reasonable to consider diesel exhaust fumes and solvents as probable confounders; however, neither of these factors were accounted for in any of the studies evaluated in detail. There is also evidence that ultraviolet (UV) radiation may increase the risk of NHL (Karipidis et al., 2007; Zhang et al., 2007). As a result, there is a support that UV radiation is also a potential confounder given the extended amount of time agricultural workers spend outside performing activities, including those associated with pesticide use. Lastly, contact with farm and other animals has been investigated as a suspected risk factor for hematopoietic and lymphoid tumors (McDuffie et al., 2002). Hypothesized mechanisms to explain this association include viral transmissions, chronic antigenic stimulation, and exposure to endotoxins, fungi, and mycotoxins. None of the aforementioned potential confounders were accounted for in the studies evaluated in detail.

3.2.5 Statistical Analyses

Statistical analyses that were appropriate to the study question and study design, supported by adequate sample size, maximized the use of available data, and were well characterized in the report were weighted most highly. Acceptable statistical methods, questionable study power or sample size, and analytical choices that resulted in the loss of information were given moderate weight. Reports with only minimal attention paid to the conduct and reporting of the statistical analyses were given the lowest weight.

3.2.6 Risk of Bias

The internal validity of the studies reviewed was judged by noting the design strategies and analytic methods used in each study to constrain or eliminate selection bias, information bias, and confounding. Selection bias can occur when the sampling of the population by the investigator yields a study population that is not representative of the exposure and outcome distributions in the population sampled. Put simply, selection bias occurs if selection of the study sample yields a different estimate of the measure of association than that which would have been obtained had the entire target population been evaluated. Although there are numerous sources of selection bias, there are several mechanisms that may have induced selection bias in the studies reviewed: low participation rates of eligible individuals due to non-responsiveness or refusal (self-selection bias); loss to follow-up (i.e., failure to retain all study participants initially enrolled in the study); and, in a case-control study, control selection bias arising because the exposure distribution in the control sample does not represent the exposure distribution of the study base (i.e., the population that gave rise to the cases or more formally, the person-time experience of that population).

Information bias (also referred to as observation bias) arises when study participants are incorrectly categorized with respect to their exposure or outcome status, or when errors arise in the measurement of exposure or outcome, in the case of continuously distributed measures. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random). Non-differential misclassification of exposure (or non-differential exposure measurement error) occurs when the probability or magnitude of error in the classification or measurement of exposure is independent of the outcome status of the study participants. Non-differential exposure measurement error typically results in a bias towards the null which may obscure any true effect of the exposure of interest. Similarly, non-differential misclassification of outcome (or outcome measurement error) occurs when the probability or magnitude of error in the assignment of outcome status or level is independent of exposure status. Non-differential outcome measurement error typically does not cause bias but does decrease the precision of effect estimates and therein inflates the width of confidence intervals. In contrast, differential exposure misclassification (or measurement error) occurs when the error in the exposure assignment is not independent of the outcome status. The mechanisms that cause non-differential misclassification in the currently reviewed literature include random errors in exposure recall from subjects or proxy respondents. The mechanisms that could induce differential misclassification include recall bias and interviewer/observer bias. Note that mismeasurement of confounders can result in residual confounding of the association of interest, even when adjustment for that confounder has been conducted in the analysis.

Studies in which major sources of potential biases were not likely to be present, studies in which potential sources of bias were present, but effectively addressed and analyzed to maximize the study validity, and studies in which sources of bias were unlikely to influence the magnitude and direction of the effect estimate were given more weight than studies where sources of bias may be present, but not addressed in the study.

3.3 Review of Quality Results

Each study was judged to be of high, moderate, or low quality in each of the six domains affecting study quality, as discussed above and in Table 3.1. The results of the quality

assessment are presented separately for each group below. The quality rankings presented are specific to the current evaluation of the carcinogenic potential of glyphosate. As noted above and in Table 3.2, several studies were not included in the ranking evaluation because they did not represent the most complete analysis. Rather, the subjects were included in a larger analysis (e.g., pooled case-control study) to produce a greater number of cases and controls (see Appendix B for visual representation of these studies). For example, Cantor *et al.* (1992) was not individually evaluated for ranking because the data from this study were pooled with data from other studies in De Roos *et al.* (2003), which was included.

3.3.1 "High" Quality Group

Three studies were given a high quality ranking: De Roos *et al.* (2005), Eriksson *et al.* (2008), and Koutros *et al.* (2013).

De Roos *et al.* (2005) was a prospective cohort study that evaluated associations between various pesticide exposures, including glyphosate, and cancer incidence for numerous solid and non-solid tumors in the AHS. The aim of the AHS is to evaluate the role of agricultural exposures in the development of cancer and other diseases in the farming community. AHS recruited 52,934 licensed private pesticide applicators along with 32,345 of their spouses between 1993 and 1997. In the first two phases of the study, the cohort also included 4,916 commercial pesticide applicators from Iowa. As a prospective analysis of the AHS cohort, information was obtained from exposed subjects at enrollment and no proxies were necessary. Exposure was evaluated as ever/never use, cumulative lifetime exposure, and intensity-weighted cumulative exposure. Due to the study design, the potential for many biases were reduced. Additionally, the study adjusted and/or considered numerous factors, including use of other pesticides. Study participants provided detailed pesticide exposure information prior to enrollment in the study and this information has been incorporated into the study evaluation by determining tertile cut points and calculating effect estimates by comparing to the lowest tertile. Additional evaluations with quartiles and quintiles were performed for cancers with elevated effect estimates in the study and for NHL. As noted earlier in this document, an analysis of the AHS cohort was recently published (Andreotti *et al.*, 2017) and the findings were considered as part of this evaluation.

Eriksson *et al.* (2008) was a population-based case-control study that recruited a consecutive series of incident cases of NHL in several regions of Sweden from physicians treating lymphoma within specified health service areas. Cases were verified pathologically and matched to randomly selected controls from the national population registry by age, sex and health service area. Exposure information was collected from exposed individuals (i.e., no use of proxy respondents) using a comprehensive questionnaire including a total work history with in depth questions about exposures to pesticides, solvents, and other chemicals. Interviewers were blinded to case/control status. The study only reported minimal demographic information on subjects (age and sex) and a table with subject characteristics (e.g., smoking status, alcohol intake, physical activity, education) that could potentially be used to adjust effect estimates was not provided. Glyphosate exposure was reported in 29 cases and 18 controls during the study period. Multivariate analyses were adjusted for co-exposure to different agents, including MCPA, "2,4,5-Y and/or 2,4-D", mercurial seed dressing, arsenic, creosote, and tar. An analysis for a potential exposure-response relationship was also conducted; however, it was not clear

whether this analysis adjusted for co-exposure to other pesticides based on the statistical methods description. The number of cases and controls were also not reported for this analysis.

Koutros *et al.* (2013) was a prospective cohort study within the AHS that evaluated the association between pesticide use and prostate cancer. Exposure information was collected from exposed subjects (no proxies necessary) through the enrollment questionnaires, as well as in a follow-up questionnaire administered 5 years after enrollment. This study evaluated the association between glyphosate and prostate cancer diagnoses from enrollment (1993-1997) through 2007 resulting in a longer follow-up time than many of the other case-control studies that utilized AHS subjects. The study used lifetime cumulative exposure and intensity-weighted cumulative exposure metrics. Analyses were also conducted using unlagged exposure and 15-year lagged exposure, which excluded the most recent 15 years of exposure for both exposure metrics. Although the effect estimate reported for glyphosate in this study was not adjusted for co-exposure to other pesticides, additional analyses were not considered necessary since there was no association observed.

3.3.2 "Moderate" Quality Group

Twenty-one case-control studies were assigned a moderate quality rating (Table 3.2). In general, these studies share many study design characteristics. Exposure information was collected from subjects and/or proxy individuals, the outcome measurement(s) utilized state/national registries and surveillance programs, appropriate statistical analyses were performed, some covariates but maybe not all relevant covariates were evaluated and/or considered, and risks of bias were minimized to some extent. Sample sizes varied across studies. Case-control studies investigating solid tumors included study populations in the United States and Canada. For non-solid tumors, study populations were located in the United States, Canada, Sweden, France, Germany, Italy, Ireland, Spain, and the Czech Republic. Although several nested case-control studies shared most of the characteristics of the AHS cohort study, these studies were primarily given a moderate quality ranking since co-exposure to other pesticides was not accounted for in the analyses.

3.3.3 "Low" Quality Group

Seven case-control and 27 cross-sectional/ecological studies were assigned a low quality ranking. All of these studies, except one case-control study (Cocco *et al.*, 2013) and one descriptive study (Koureas et al., 2014), were not subjected to a detailed evaluation because they did not report a quantitative measure of an association between glyphosate exposure and a cancer outcome, did not collect information on glyphosate exposure from all subjects, and/or did not evaluate risk to a cancer outcome (Appendix D). In many instances, effect estimates were reported only for total pesticide exposure. Additionally, exposure was assumed and glyphosate-specific exposure information was not collected. In other studies, the aim of the study was to assess exposure methods for epidemiological studies and/or to evaluate the impact of exposure misclassification; therefore, there was no evaluation of a cancer outcome.

It should be noted that some of the studies assigned a low quality ranking in the current evaluation were included in the recent evaluation by IARC. There were a number of descriptive studies that evaluated the genotoxicity in human populations; however, these studies did not

meet the criteria for inclusion in the ranking as described in Section 3.2 and Figure 3.1. In most instances, these studies reported effect estimates for total pesticide exposure and/or assumed glyphosate exposure without collecting glyphosate-specific exposure information. For case-control studies, Cocco et al. (2013), Dennis et al. (2010) and Ruder et al. (2004) were included in the 2015 IARC evaluation, but were not considered informative in the current evaluation.

Detailed evaluations were not performed in the current evaluation for Dennis et al. (2010) and Ruder et al. (2004) because a quantitative measure of an association between glyphosate and a cancer outcome was not reported. Cocco et al. (2013) received a detailed evaluation and was assigned a low quality ranking. This case-control study, which evaluated lymphoma risk across six European countries, was not considered informative due to a combination of numerous limitations in the study. The sample size of the study was low with only four cases and two controls exposed to glyphosate. Control ascertainment was not consistent across countries, with a mix of hospital- and population-based controls used. The overall participation rate for population-based controls was found to be much lower than the overall participation rates of the cases or hospital-based controls. Lastly, the study was limited to ever/never use of glyphosate and did not adjust for confounders, in particular co-exposure to other pesticides. Although this study was included in the IARC evaluation, IARC also stated that the study had very limited power to assess the effects of glyphosate on risk of NHL.

The other study subjected to a detailed evaluation and assigned a low quality ranking was Koureas *et al*. (2014). This cross-sectional study evaluated the association between glyphosate exposure and oxidative DNA damage in 80 Greek pesticide sprayers. Although the study reported a non-statistically significant effect estimate for glyphosate, it is limited in its ability to contribute to the overall evaluation of the carcinogenic potential of glyphosate. The effect estimate was not adjusted for any standard covariates or potential confounders, including co-exposure to other pesticides. The sample size of the study was questionable. There were 80 subjects, but the number exposed to glyphosate was not reported. The outcome is measured using an immunoassay that is less specific for measuring the biomarker of interest than other available analytical methods. Lastly, the study evaluates primary DNA damage, but does not measure the consequence of genetic damage. An increase in oxidative DNA damage may lead to cell death or initiate DNA repair rather than lead to a mutation.

Due to the limitations in the studies assigned a low quality ranking, they do not provide reliable information to evaluate associations between glyphosate exposure and cancer outcomes. Therefore, the remaining sections of this document do not further discuss these studies except to note when a study is included in meta-analyses.

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
Alavanja *et al.* (2003)	This study was not included in the study quality ranking because the data were used in the updated analysis by Koutros *et al.* (2013).						
Andreotti *et al.* (2009)	Nested Case-control	Questionnaire answered by subjects at study enrollment followed by take-home questionnaire; examined exposure for glyphosate as ever/never, and intensity-weighted cumulative exposure days; spouses either self-administered questionnaire (81%) or telephone interview (19%)	State cancer registries without histopathological verification; exclusion of subjects with prevalent cancer at enrollment; follow-up ~ 9 years	Adjusted for age, smoking, and diabetes for both exposure metrics as well as applicator type forever/never exposure metric No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI	Exposure misclassification particularly for spouses, low response rate to take-home questionnaire (40%) but unclear if affected cases and controls differently, insufficient power for pesticide exposure interactions	Moderate
Band *et al.* (2011)	Population-based case-control Males only	Self-administered questionnaire answered by subjects or proxies for deceased subjects requesting work history and demographic information; use of a job exposure matrix to estimate exposure to pesticides	Cancer registry with histopathological verification; excluded farmers that worked all outside of British Columbia; included prostate cancer cases prior to the PSA era	Adjustment for alcohol consumption, cigarette years, education level, pipe years, and respondent type. Marital status and ethnicity not significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain ORs and 95% CIs	Recall bias, use of proxy for deceased, exposure misclassification, participation rates cited from another study, use of cancer patients as controls (excluding lung and unknown cancer)	Moderate
Brown *et al.* (1990)	Pooled population-based case-control Males only	In-person interviews using standardized questionnaire with subjects or proxies for deceased/incapacitated; supplementary questionnaire administered by telephone for Iowa subjects to obtain more	State cancer registry (Iowa) and special surveillance network including hospitals and pathology laboratories (Minnesota); cases ascertained retrospectively and prospectively (2 years after start of study);	Adjusted for vital status, age, state, ever used tobacco daily, close relative with lymphopoietic cancer, nonfarming job related to risk of leukemia in the study, exposure to substances related to risk in this study	Unconditional logistic models to obtain OR and 95% CI; questionable sample size (15 cases)	Recall bias; exposure misclassification, use of proxy respondents	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
		detailed information from those indicating pesticide use	~26% of cases deceased or too ill when identified and ~15% deceased or too ill at time of interview; histopathological verification by pathologists	(benzene, napthalene, hair dyes) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Brown *et al.* (1993)	Population-based case-control Males only	In person interviews with standardized questionnaire to obtain detailed information on farm activities and use of pesticides from subjects or proxies	State cancer registry (Iowa) ascertained retrospectively and prospectively (2 years after start of study); ~26% of cases deceased or too ill when identified and ~15% deceased or too ill at time of interview; histopathological verification by pathologists	Adjusted for vital status and age; smoking and education evaluated and not found to be significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Logistic models to obtain OR and 95% CI; questionable sample size (11 cases)	Recall bias; exposure misclassification, use of proxy respondents	Moderate
Cantor *et al*. (1992)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by De Roos *et al.* (2003).						
Carreon *et al.* (2005)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Yiin *et al.* (2012).						
Cocco *et al*. (2013)	European multi-center case-control Hospital-based and population-based (mixed for 2 countries, only hospital-based for the rest)	Trained interviewers conducted in person interviews using structured questionnaire answered by subjects; those identified as agricultural worker on questionnaire given subsequent questions about pesticide use, crops, etc.	Surveillance centers, 20% of slides from each center reviewed by pathologist	Adjustment for age, sex, education, and center. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain ORs and 95% CIs; Low sample size (4 cases, 2 controls)	Recall bias, selection bias (low response rate for population-based controls and differed from cases), exposure misclassification, mix of hospital- and population-based controls,	Low
De Roos *et al*. (2003)	Population-based case-control Males only Pooled analysis of	Interviews with subjects or proxy for deceased subjects. Different interview techniques across states. One study collected information on	State cancer registries (one state chose a random sample, other states chose all cases), surveillance programs, and hospitals without	Adjustment for age, study site, and other pesticides. First degree relative with haematopoietic	Logistic regression and hierarchical regression to obtain ORs and 95% CIs	Recall bias, exposure misclassification, , use of proxy for deceased, , varying quality of questionnaire/interview techniques across studies	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
	Cantor *et al.*, 1992; Hoar *et al.*, 1986; Zahm *et al.*, 1990	pesticide use and then followed-up with questions on selected specific pesticides, another study had a direct question about a selected list of specific pesticides, and the last study used an open ended question without prompting for specific pesticides	histopathological verification	cancer, education, and smoking not found to be important confounders. No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
De Roos *et al*. (2005)	Prospective cohort (licensed pesticide applicators)	Questionnaire answered by subjects at enrollment and with subsequent take-home questionnaire; examined exposure as ever/never, cumulative lifetime days, and intensity-weighted cumulative exposure days	State cancer registries without histopathological verification; follow-up ~7 years	Adjustment for state of residence, age, education, smoking history, alcohol consumption, family history of cancer, use of other common pesticides No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Poisson regression to obtain RRs and 95% CIs	Major sources of potential biases unlikely, potential exposure misclassification due to any changes in exposure since enrollment, follow-up period may be limited	High
Engel *et al.* (2005)	Nested case-control Females only	Take-home questionnaire from spouses of enrolled applicators used to obtain farm exposures, general health information, and reproductive health history; Information obtained from applicators used as measure of possible indirect exposure to spouses	State cancer registries identifying malignant breast cancer; ~5 years average follow-up time	Adjusted for age, race and state. Evaluated BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause, family history of breast cancer, physical activity, smoking, alcohol consumption, fruit and vegetable consumption and education but none	Poisson regression to obtain RRs and 95% CIs	Exposure misclassification, exposure to other pesticides (however no association observed), lack of information on length of marriage could result in overestimating exposure based on husband	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
				found to be significant No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Eriksson *et al*. (2008)	Population-based case-control	Questionnaire answered by subjects; follow-up by phone if incomplete answers; excluded exposures that occurred during the same calendar year and year before diagnosis (cases) or enrollment (controls); minimal demographic information reported	Physicians treating lymphoma within specified health service areas and verified by pathologists	Adjustment for age, sex, year of diagnosis/enrollment, as well as exposure to other pesticides in multivariate analyses. Not stated what adjustments were made for other pesticides in latency analyses. No adjustment other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression and multivariate analyses to obtain ORs and 95% CIs; not clear how multivariate was performed; questionable sample size (29 cases, 18 controls); also included analysis of ≤10 vs. >10 years exposure	Recall bias, exposure misclassification, lack of subject demographics/ characteristics (e.g., smoking, alcohol consumption, race, etc)	High
Flower *et al.* (2004)	Nested case-control	Questionnaire answered by applicators at enrollment; spouses enrolled through a questionnaire brought home by applicator; females (applicators and spouses) were asked to complete a questionnaire on female and family health that collected information on children born during or after 1975	State cancer registry to identify childhood cancer cases (diagnosed from birth through 19 yrs of age) for children of parents enrolled; hybrid prospective/retrospective ascertainment; excluded female applicators	Child's age at parent's enrollment was included in model; parental age at child's birth, child's sex, child's birth weight, history of parental smoking, paternal history of cancer, and maternal history of miscarriage were evaluated but not found to be significant and not included in model No adjustment for co-	Logistic regression to obtain OR and 95% CI; calculated standardized incidence ratios to compare observed number of childhood cancer cases identified to the expected number; low/questionable sample size (6 parental cases, 13 maternal cases)	Exposure misclassification, lack of timing data to determine if exposure occurred prior to conception or during pregnancy, exposure to other pesticides (however no association observed and lack of power for adjustment)	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
				exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Hardell and Eriksson (1999)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Hardell *et al.* (2002).						
Hardell *et al*. (2002)	Population-based case-control Males only Pooled analysis of Hardell and Eriksson 1999 and Nordstrom *et al.*, 1998	Questionnaire answered by subjects or proxy for deceased subjects to obtain complete working history and exposure to different chemicals; follow-up with interview for clarification	Registries with histopathological verification	Adjustment for age, vital status, and county (by matching). Exposure to other pesticides in multivariate analysis. No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI (univariate and multivariate analyses). Questionable sample size (8 cases/8 controls)	Recall bias, exposure misclassification, use of proxy for deceased	Moderate
Hohenadel *et al*. (2011)	This study was not included in the study quality ranking because a more complete analysis was conducted by McDuffie *et al.* (2001).						
Kachuri *et al.* (2013) (extended analysis of Pahwa *et al.* 2012)	Population-based case-control Males only	Questionnaire answered by subjects or proxies; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 36.55% of samples	Adjustment for age, province, selected medical conditions, family history of cancer, use of proxy respondent, smoking status No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls, use of proxy respondents	Moderate
Karunanayake *et al.* (2012)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15%	Cancer registries or hospital in 6 Canadian provinces with histopathological verification for 49% of samples; difficulty recruiting control	Adjusted for age, province of residence, and significant medical history variables No adjustment for co-	Conditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
		random sample of those who did not; exposure based on lifetime exposure to glyphosate	participants for older age groups	exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)		controls, unable to evaluate Epstein-barr virus exposure	
Koureas *et al*. (2014)	Cross-sectional	Questionnaire answered by pesticide sprayers	Genomic DNA extracted from peripheral blood samples and oxidation by-product 8-hydroxydeoxyguanosine (8-OHdG) was determined by enzyme immunoassay; more specific methods (HPLC, GC-MS) are available for measurement	No adjustments. In univariate, occupational exposure, sex and alcohol consumption were statistically significant while DAP concentrations and smoking were not.	For univariate, chi-square test used to obtain RR and 95% CI; 8-OHdG levels transformed into binary variables (categorized as high and low using the 75th percentile cut-off); unknown number of exposed and unexposed cases (questionable sample size possible given total number of subjects is only 80)	Recall bias, did not control for risk factors identified as statistically significant for univariate analysis, does not measure the consequence of genetic damage	Low
Koutros *et al.* (2013)	Prospective cohort Males only	Questionnaire answered by subjects at study enrollment; examined exposure as cumulative lifetime days and intensity-weighted cumulative exposure days	State cancer registries with histopathological verification; total and aggressive prostate cancers evaluated	Adjustment for age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Poisson regression to obtain RRs and 95% CIs; also included unlagged vs. lagged analysis	Exposure misclassification	High
Landgren *et al*. (2009)	Nested case-control[a] Males only	Questionnaire answered by subjects at enrollment in AHS cohort and subsequent take-home questionnaire to collect	Venous blood collected from antecubital vein and analyzed for MGUS; same method as used for controls group in	Adjusted for age and education level Association with other pesticides examined	Logistic regression models to obtain OR and 95% CI comparing to population-based	Exposure misclassification, control group not from geographical area (used control group with	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
		information on 50 pesticides; occupational expoures, medical histories, and lifestyle factors updated with 5-year follow-up interview; subjects with prior history of lymphoproliferative malignancy excluded	Minnesota	and not found to be significant so no adjustment performed No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	screening study in Olmsted County, Minnesota; questionable sample size (27 cases; 11 controls)	similar demographics from Minnesota)	
Lee *et al*. (2004a)	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by De Roos *et al*. (2003).						
Lee *et al*. (2004b)	Population-based case-control White males and females only	Subjects or proxies were interviewed by telephone; those living/working on a farm asked for detailed history of pesticide use and farming information	State cancer registry or review of discharge diagnosis and pathology records at 14 hospitals; only newly diagnosed cases with confirmed adenocarcinoma of stomach or esophagus retained; controls randomly selected from a prior study conducted in geographical area	Adjusted for age and sex; evaluated BMI, smoking, alcohol consumption, educational level, family history of stomach or esophageal cancer, respondent type, dietary intake of particular vitamins and minerals, protein, and carbohydrates (included in model if changed value of OR by more than 10%) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain OR and 95% CI; questionable sample size (12 cases for stomach; 12 cases for esophagus)	Recall bias, exposure misclassification, use of proxy respondents, control selection	Moderate
Lee *et al*. (2005)	Population-based case-control	Questionnaire and/or interview with subject or proxy individuals to collect information on use of specific pesticides; telephone follow-up for unclear responses	Referral by hospitals or through state cancer registries with histopathological verification; controls selected from a previous study	Adjusted for age and respondent type; evaluated history of head injury, marital status, education level, alcohol consumption, medical history of diabetes mellitus,	Unconditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, large number of proxy respondents, control selection (historical control group from another cancer evaluation, differences in	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
				dietary intake of α- and β-carotene, and dietary fiber (included in model if changed value of OR by more than 10%) No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)		exposure time period evaluated, needed to add younger controls, exposure information collected for different time periods for cases vs. controls)	
Lee *et al*. (2007)	Nested case-control	Questionnaire answered by subjects at enrollment in AHS cohort and subsequent take-home questionnaire to collect information on 50 pesticides	State cancer registries without histopathological verification; follow-up ~ 7 years	Adjustment for age, smoking, state, total days of pesticide application No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional multivariate logistic regression to obtain OR and 95% CI	Exposure misclassification, limited data on dietary factors, NSAID drug use and family cancer history	Moderate
McDuffie *et al*., 2001	Population based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospital in 6 Canadian provinces with histopathological verification for 84% of samples; ascertainment of cases stopped in each province once target numbers were reached	Adjustment for age, province, and significant medical variables (including history of cancer in study participants and family history). No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, relatively low participation rates	Moderate
Nordstrom *et al*., 1998	This study was not included in the study quality ranking because the data were used in the pooled analysis conducted by Hardell *et al.* (2002).						
Orsi *et al*., 2009	Hospital-based case-control	Data collection in 2 stages: 1) self-	Hospital catchment area with histopathological/	Adjustment for age, center, and	Unconditional logistic regression	Recall bias, exposure misclassification,	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
	Males only (occupationally exposed)	administered questionnaire on socioeconomic characteristics, family medical history, and lifelong residential and occupational histories and more specific information for each job held for at least 6 months, and 2) face-to-face interview with trained staff (blinded) using standardized questionnaire	cytological verification Controls were hospital based with no prior history of lymphoid neoplasms, excluding patients with cancer or a disease directly related to occupation, smoking or alcohol abuse (but history of any of these did not prevent selection as a control)	socioeconomic category. Education and housing not found to impact results. Flu immunization, previous history of mononucleosis, skin type, smoking, and drinking did not change results. Evaluated particular crops and animal husbandry as well. No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	to obtain OR and 95% CI. Questionable sample size (12 cases/24 controls)	hospital-based controls	
Pahwa *et al*. (2011)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those who did not; exposure based on lifetime exposure to glyphosate	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 30% of samples	Adjustment for age group, province of residence, and statistically significant medical history variables No adjustment for co-exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Conditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls	Moderate
Pahwa *et al*. (2012)	Population-based case-control Males only	Questionnaire answered by subjects; pesticide use collected via detailed telephone interview on all participants with 10+ hours of pesticide use during lifetime and 15% random sample of those	Cancer registries or hospitals in 6 Canadian provinces with histopathological verification for 36.5% of samples	Adjustment for age group, province of residence, and statistically significant medical history variables No adjustment for co-	Conditional logistic regression to obtain OR and 95% CI; trends examined using multiple logistic regression	Recall bias, exposure misclassification, control selection based on three different sources depending on province of residence, low participation rates among controls	Moderate

Table 3.2. Summary of Study Design Elements Impacting Study Quality Assignment and Overall Ranking.							
Journal Article	**Study Design**	**Exposure Assessment**	**Outcome Assessment**	**Confounder Control**	**Statistical Analyses**	**Risk of (Other) Bias**	**Overall Ranking**
		who did not; exposure based on lifetime exposure to glyphosate		exposure to other pesticides or other potential confounders (e.g., solvents, diesel fumes, UV radiation)			
Yiin *et al.* (2012)	Population-based case-control Pooled analysis of men with women analyzed in Carreon *et al*. (2005)	Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Cases referred by physicians or through state cancer registries with histopathological verification; controls matched within state, but not county of residence	Adjustment for age, education, sex, and , sex, and farm pesticide exposure (yes/no) No adjustment for other potential confounders (e.g., solvents, diesel fumes, UV radiation)	Unconditional logistic regression to obtain ORs and 95% CIs	Acknowledge other sources of bias. Recall bias, exposure misclassification, control selection (low number of deceased controls obtained)	Moderate

[a] Mixed methods used in the Landgren et al (2009) study, with cross-sectional study design used to calculate prevalence rates comparing the AHS to a reference population MN. Pesticide risk estimates (including glyphosate) calculated using nested case-control approach, comparing AHS exposed/unexposed (ever/never) study participants.

3.4 Assessment of Epidemiological Studies for Relevance to Analysis

Using the criteria summarized in Section 3.2, a total of 63 individual literature studies were identified in the literature review and were judged as high, moderate, or low quality. The data from 7 of these studies were used in pooled analyses by other studies; therefore, they were not subjected to detailed evaluation. Overall, 3 studies, 19 studies, and 34 studies were assigned high, moderate, or low rankings, respectively. All of the high and moderate quality studies were considered relevant to the current evaluation. Additionally, the findings of a recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) have been considered in this evaluation, when appropriate.

The majority of the studies were case-control studies evaluating a wide-range of cancers in the United States and Canada. There were several case-control studies from Canada that utilized the same study population (Kachuri *et al.*, 2013; Karunanayake *et al.*, 2012; McDuffie *et al.*, 2001; Pahwa *et al.,* 2011; Pahwa *et al.*, 2012). In a similar fashion, numerous studies in the United States were nested case-control studies, where the AHS cohort served as the source population for selecting cases and controls (Andreotti *et al*., 2009; Engel *et al*., 2005; Flower *et al*., 2004; Landgren *et al*., 2009; Lee *et al*., 2007). In these studies, a subset of the AHS cohort was selected based on their outcome status for a particular cancer and exposure information was used from the AHS enrollment questionnaire and/or during follow-up interviews. Nested case-control studies allow for testing of hypotheses not anticipated when the cohort was initially assembled. In the AHS prospective cohort studies (De Roos *et al*., 2005; Koutros *et al*., 2013; Andreotti *et al.*, 2017), exposure and demographic information were also obtained from the questionnaires at enrollment; however, subjects were enrolled prior to developing cancer outcomes of interest. Subjects were then followed from enrollment to a subsequent time point to determine if subjects developed cancer outcomes of interest. As such, all available subjects in the cohort are included in the evaluation of whether there was an association between a risk factor (e.g., glyphosate exposure) and outcome.

The moderate studies included a varying degree of control for confounding and biases across studies. As moderate studies, they encompass a combination of strengths and limitations. In particular, important factors that impacted the quality assessment for these studies included whether there was adjustment for known confounders, identification of control selection issues, sample size issues, and length of follow-up. As noted previously, most people in these epidemiological studies used pesticides occupationally and were exposed to multiple pesticides over their working lifetime. Therefore, exposure to other pesticides is a particularly important factor to adjust for and studies that made this adjustment were given more weight than those that did not. Similarly, control selection issues were noted in a few studies and were given less weighting than those without control selection issues. The issues ranged from concerns using hospital-based controls, using different population sources to ascertain controls within the same study, and appropriateness of using controls ascertained for another research question. Numerous studies were limited by small sample sizes, which results in large confidence intervals and reduces the reliability of the results to demonstrate a true association. Studies demonstrating low or questionable sample size were therefore given less weighting. Lastly, the length of follow-up time varied across studies.

3.5 Summary of Relevant Epidemiological Studies

A summary of the relevant studies evaluating the association between glyphosate exposure and cancer are discussed below. Results of the studies reporting data on glyphosate exposure and solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 3.3. Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.4. For study details, see Table 3.2 above and Appendix C.

3.5.1 Solid Tumor Cancer Studies

(1) Cancer at Multiple Sites from the AHS Cohort

De Roos *et al*., (2005) evaluated associations between glyphosate exposure and cancer incidence of all cancers combined in the AHS cohort study and did not find an association [ever/never use relative risk ratio (RR) =1.0 with 95% confidence interval (CI) of 0.90–1.2) when adjusting for age, demographic and lifestyle factors, and exposure to other pesticides]. In addition, De Roos *et al*., 2005 evaluated cancer at specific anatomical sites. Along with several nested case-control studies, no statistical evidence of an association with glyphosate was observed at any specific anatomical site (Table 3.3). Specifically, AHS researchers reported no evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al*., 2005), colon (De Roos *et al*., 2005; Lee *et al*., 2007), rectum (De Roos *et al*., 2005; Lee *et al*., 2007), lung (De Roos *et al*., 2005), kidney (De Roos *et al*., 2005), bladder (De Roos *et al*., 2005), pancreas (De Roos *et al*., 2005; Andreotti *et al*., 2009), breast (Engel *et al*., 2005), prostate (De Roos et al., 2005; Koutros *et al*., 2013) or melanoma (De Roos *et al*., 2005). The adjusted RR or odds ratio (OR) and 95% CI for these studies are provided in Table 3.3.

Findings from the recently published analysis of the AHS cohort (Andreotti *et al*., 2017) with a longer follow-up period than De Roos *et al.* (2005) also did not find associations between glyphosate exposure and incidence of all cancers based on intensity-weighted lifetime days of glyphosate use. Furthemore, there was no evidence of an association between glyphosate use and cancers of the oral cavity, colon, rectum, pancreas, lung, melanoma, prostate, testes, bladder, or kidney. Although there was evidence of a significant positive association in one quartile only relative to intensity-weighted lifetime days of glyphosate exposure for pancreatic and lung cancer, there was no evidence of a significant positive association in any other quartile for either cancer type and the exposure-response trends were not statistically significant. As a result, these isolated findings were not considered suggestive of an association.

(2) Prostate Cancer

In a Canadian population-based study (Band *et al.*, 2011), researchers reported non-statistically significant elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). There was no adjustment made for exposure to other pesticides. This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. The AHS related studies (De Roos *et al*., 2005; Koutros *et al*., 2013; Andreotti *et al*., 2017), reflect PSA-era cases

(i.e., cases which are typically identified at an earlier stage in the progression of the disease) and also did not identify an association with prostate cancer.

(3) Brain (Glioma) Cancer

Lee *et al*. (2005) investigated the association between brain cancer with farming and agricultural pesticide use. Matching for age, sex, vital status, and region, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use by male farmers; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was a potential factor in this study. Furthermore, there was no adjustment for co-exposure to other pesticides and issues noted with control selection.

A population-based case-control study evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Yiin *et al*., 2012). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), Yiin *et al*. (2012) observed no statistical evidence of an association with glyphosate with effect estimates roughly equal to the null value following adjustment for age, education, sex, and use of other pesticides (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73).

(4) Stomach and Esophageal Cancer

In a population-based case-control study in eastern Nebraska, Lee *et al*. (2004b) investigated pesticide use and stomach and esophageal adenocarcinomas. There was no association observed between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4) after adjustment for age and sex. No adjustment was made for exposure to other pesticides.

(5) Soft Tissue Sarcoma

A Canadian case-control study (Pahwa *et al*., 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate after adjustment for age, province of residence, and medical history variables (OR=0.90; 95% CI= 0.58–1.40); however, control selection issues were noted, including low response rate and selection from three different sources depending on the province of residence.

(6) Total Childhood Cancer

Flower *et al*. (2004), a nested case-control study in the AHS cohort, examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate (OR=0.84; 95% CI= 0.35–2.54). The models adjusted for the child's age at the time of parents' enrollment. There was no adjustment for exposure to other pesticides.

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
All Cancers Combined					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.9-1.2)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.0 (0.9-1.1) 1.0 (0.9-1.1)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.9 (0.8-1.0) 0.9 (0.8-1.1)	Age, demographic and lifestyle factors, and other pesticides[b]
Lung					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	0.9 (0.6-1.3)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.9 (0.5-1.5) 0.7 (0.4-1.2)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.1 (0.7-1.9) 0.6 (0.3-1.0)	Age, demographic and lifestyle factors, and other pesticides[b]
Oral Cavity					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.5-1.8)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.8 (0.4-1.7) 0.8 (0.4-1.7)	Age, demographic and lifestyle factors, and other pesticides[b]

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.1 (0.5-2.5) 1.0 (0.5-2.3)	Age, demographic and lifestyle factors, and other pesticides[b]
Kidney					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.6 (0.7-3.8)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.6 (0.3-1.4) 0.7 (0.3-1.6)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.3 (0.1-0.7) 0.5 (0.2-1.0)	Age, demographic and lifestyle factors, and other pesticides[b]
Bladder					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.5 (0.7-3.2)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.0 (0.5-1.9) 1.2 (0.6-2.2)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.5 (0.2-1.3) 0.8 (0.3-1.8)	Age, demographic and lifestyle factors, and other pesticides[b]

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
Melanoma					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.6 (0.8-3.0)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.2 (0.7-2.3) 0.9 (0.5-1.8)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.6 (0.3-1.1) 0.7 (0.3-1.2)	Age, demographic and lifestyle factors, and other pesticides[b]
Colon					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.4 (0.8-2.2)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.4 (0.9-2.4) 0.9 (0.4-1.7)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 0.8 (0.5-1.5) 1.4 (0.8-2.5)	Age, demographic and lifestyle factors, and other pesticides[b]
Lee *et al.* (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.0 (0.7-1.5)	Age, smoking, state, total days of pesticide application
Rectum					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.3 (0.7-2.3)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.3 (0.7-2.5) 1.1 (0.6-2.3)	Age, demographic and lifestyle factors, and other pesticides[b]

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.0 (0.5-2.0) 0.9 (0.5-1.9)	Age, demographic and lifestyle factors, and other pesticides[b]
Lee *et al.* (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.6 (0.9-2.9)	Age, smoking, state, total days of pesticide application
Colorectal					
Lee *et al.* (2007)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.2 (0.9-1.6)	Age, smoking, state, total days of pesticide application
Pancreas					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	0.7 (0.3-2.0)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 1.6 (0.6-4.1) 1.3 (0.5-3.6)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 2.5 (1.0-6.3) 0.5 (0.1-1.9)	Age, demographic and lifestyle factors, and other pesticides[b]
Andreotti *et al.* (2009)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	1.1 (0.6-1.7)	Age group, cigarette smoking, diabetes, and applicator type
			Intensity-Weighted Exposure Days (by control median): ≤184 ≥185	1.4 (0.9-3.8) 0.5 (0.2-1.3)	Age group, cigarette smoking, and diabetes
Prostate					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	1.0 0.9 (0.7-1.1) 1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides[b]

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	1.0 1.0 (0.8-1.2) 1.1 (0.9-1.3)	Age, demographic and lifestyle factors, and other pesticides[b]
Koutros *et al.* (2013)[c]	Prospective cohort	USA: Iowa and North Carolina	Intensity-Weighted Cumulative Exposure Days (by quartile): Q1 Q2 Q3 Q4	Total prostate cancer: 0.91 (0.79-1.06) 0.96 (0.83-1.12) 1.01 (0.87-1.17) 0.99 (0.86-1.15)	Age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter
			Intensity-Weighted Cumulative Exposure Days (by quartile): Q1 Q2 Q3 Q4	Aggressive prostate cancer: 0.93 (0.74-1.16) 0.91 (0.73-1.13) 1.01 (0.82-1.25) 0.94 (0.75-1.18)	Age, state, race, smoking, fruit servings, family history of prostate cancer, and leisure time physical activity in the winter
Band *et al.* (2011)	Case-Control	Canada: British Columbia	Ever/never	1.36 (0.83-2.25)	Alcohol consumption, cigarette years, education level, pipe years, and respondent type
Esophagus					
Lee *et al.* (2004b)	Case-Control	USA: Nebraska	Ever/never	0.7 (0.3-1.4)	Age and sex
Stomach					
Lee *et al.* (2004b)	Case-Control	USA: Nebraska	Ever/never	0.8 (0.4-1.5)	Age and sex
Breast					
Engel *et al.* (2005)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	Wives who apply pesticides: 0.9 (0.7-1.1) Wives who never used pesticides: 1.3 (0.8-1.9)	Age, race, and state of residence
Soft Tissue Sarcoma					
Pahwa *et al.* (2011)	Case-Control	Canada	Ever/never	0.90 (0.58-1.40)	Age group, province of residence, and statistically significant medical history variables

Table 3.3. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Study Location**	**Exposure Metric**	**Adjusted Effect Estimate: RR or OR (95% CI)[a]**	**Covariate Adjustments in Analyses**
Brain (glioma)					
Lee *et al.* (2005)	Case-Control	USA: Nebraska	Ever/never	Overall: 1.5 (0.7-3.1) Self-reported: 0.4 (0.1-1.6) Proxy respondents: 3.1 (1.2-8.2)	Age for overall analysis; age and respondent type for other analyses
Yiin *et al.* (2012)	Case-Control	USA: Iowa, Michigan, Minnesota, and Wisconsin	Ever/never	House/garden use: 0.98 (0.67-1.43) Non-farm jobs: 0.83 (0.39-1.73)	Age, education, sex, and use of other pesticides
Total Childhood					
Flower *et al.* (2004)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	Maternal use: 0.61 (0.32-1.16) Paternal use: 0.84 (0.35-2.34)	Child's age at enrollment

[a] Some studies report multiple quantitative risk measurements. This table reports the most highly adjusted quantitative measurements.
[b] De Roos *et al.* (2005) excluded subjects missing covariate data for demographic and lifestyle factors and exposure to other pesticides; therefore, the number of subjects included in each analysis varies.
[c] Effect estimates for glyphosate reported in the supplemental web material for Koutros *et al.* (2013).

3.5.2 Non-Solid Tumor Cancer Studies

(1) Leukemia

De Roos *et al*. (2005) reported no association between leukemia and glyphosate-exposed (ever/never used) pesticide applicators in the AHS cohort. For applicators with the full data set (54,315), the RR was 1.1 (95% CI=0.6–2.4) with only adjustment for age. In the fully adjusted model, the RR was similar (RR=1.0; 95% CI=0.5–1.9). The number of participants included in the adjusted analysis was lower (n=40,716) due to the exclusion of subjects with missing covariate data. Effect estimates using cumulative lifetime exposure and intensity-weighted cumulative exposure were also found to be non-statistically significant and did not demonstrate a trend with increasing exposure. In the recently published analysis of the AHS cohort with a longer follow-up period (Andreotti *et al*., 2017), there was no association reported between chronic lymphocytic leukemia/small lymphocytic lymphoma and chronic myeloid leukemia. For acute myeloid leukemia, an elevated but non-statistically significant association was reported in only one quartile relative to glyphosate exposure; however, there was a low number of observed cases in each of the quartiles and the overall trend was not significant. There are no other studies available evaluating acute myeloid leukemia. Given the limitations of the acute myeloid leukemia analysis, the agency will continue to follow the literature regarding the association between glyphosate exposure and risk of acute myeloid leukemia.

In a population-based case-control study in Iowa and Minnesota, Brown *et al*. (1990) did not observe an association with the ever-use of glyphosate (OR=0.9; 95% CI=0.5–1.6). A limitation in the study was the low number of cases exposed to glyphosate (n=15). Adjustments were made for several covariates, including vital status, age, tobacco use, family history of lymphopoietic cancer, high risk occupations, and high risk exposures; however, no adjustment was made for exposure to other pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and leukemia using 3 studies (De Roos *et al*., 2005; Brown *et al*., 1990; and Kaufman *et al.,* 2009). I^2 values were reported, which represented the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. A meta-risk ratio of 1.0 (95% CI=0.6-1.5) was obtained with an I^2 value of 0.0%, indicating consistency across the data sets. It should be noted that this analysis included data from Kaufman *et al.* (2009), which is not considered in the current evaluation because it was assigned a low quality ranking because a quantitative measure of an association between glyphosate and a cancer outcome was not reported for that study.

(2) Multiple Myeloma

In a follow-up analysis of the study population from Iowa and Minnesota used in Brown *et al.* (1990), Brown *et al.* (1993) investigated whether pesticide use was related to multiple myeloma. Among men in Iowa, the authors observed a non-statistically significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6; 11 exposed cases); however, no adjustment was made for exposure to other pesticides. The authors cautioned that while the study may lend

support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al*. (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on 32 multiple myeloma cases observed in the AHS cohort. For applicators with the full data set, the RR was 1.1 (95% CI=0.5–2.4) with only adjustment for age. In the fully adjusted model excluding subjects with missing covariate data, there was a non-statistically significant elevated risk following adjustment for age, demographic and lifestyle factors, and exposure to other pesticides (RR=2.6; 95% CI=0.7–9.4). The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses or may be due to a confounder or effect modifier that is prevalent among the subgroup and has not been accounted for in the analyses. When exposure data were also stratified by tertiles with the lowest tertile of exposure as the referent category, trend analyses were not statistically significant. Non-statistically significant elevated RRs of 1.9 (95% CI: 0.6-6.3) and 2.1 (95% CI: 0.6-7.0) were estimated for the highest tertile of both cumulative and intensity-weighted exposure days, respectively. The study authors did note that small sample size precluded precise estimation (n=19 for adjusted analyses). When using never exposed as the referent category, the trend analysis was again non-statistically significant, but the RRs ranged from 2.3 (95% CI: 0.6-8.9) to 4.4 (95% CI: 1.0-20.2) from the lowest tertile to the highest tertile, respectively. When stratified by quartiles, a statistically significant trend is achieved and the RR increased to 6.6 (95% CI: 1.4-30.6); however, the authors noted that the cases were sparsely distributed for these analyses. In the recently published analysis of the AHS cohort with a longer follow-up period and 88 exposed cases (Andreotti *et al*., 2017), there was no association observed between glyphosate exposure and multiple myeloma.

Sorahan (2015)[12] re-analyzed the AHS data reported by De Roos *et al*. (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Using Poisson regression, risk ratios were calculated without excluding subjects with missing covariate data. When adjusted for age and sex, the RR for ever-use of glyphosate was 1.12 (95% CI of 0.5–2.49). Additional adjustment for lifestyle factors and use of other pesticides did not have a large impact (RR=1.24; 95% CI=0.52–2.94). The authors concluded that the disparate findings in De Roos *et al.* (2005) could be attributed to the use of a restricted dataset that was unrepresentative.

Landgren *et al*. (2009), within the AHS study population, also investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (MGUS). MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe an association with glyphosate use and MGUS using subjects from the AHS cohort (OR=0.50; 95% CI=0.20–1.0). No adjustment was made for exposure to other pesticides.

In a population-based case-control study (Pahwa *et al*., 2012) among men in six Canadian provinces, a non-statistically significant elevated odds of multiple myeloma was reported in relation to glyphosate use (OR=1.22; 95% CI = 0.77–1.93), based upon 32 glyphosate exposed

[12] Funded by Monsanto

multiple myeloma cases and 133 controls. There was no adjustment for exposure to other pesticides. In an extended analysis of these data, Kachuri *et al*. (2013), using the same Canadian study population, further explored multiple myeloma in relation to days per year that glyphosate was used. Adjustment for exposure to other pesticides was also not performed in this study. For ever-use, there was a slight non-statistically significant increased odds ratio (OR=1.19; 95% CI=0.76–1.87). For light users (>0 and ≤2 days/year), there was no association (OR=0.72; 95% CI = 0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-statistically significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). Similar results were obtained when proxy respondents were excluded from the analysis. The low number of cases and controls exposed to glyphosate, particularly when exposed subjects were divided into light and heavy users, was a limitation of the study. It would be expected that effect estimates would be reduced if adjustment for co-exposure to other pesticides had been performed.

In a hospital-based case-control study conducted by Orsi *et al*. (2009) in France, 56 multiple myleoma cases and 313 age- and sex-matched controls were identified. A non-statistically significant elevated risk was observed (OR=2.4; 95% CI=0.8–7.3; 5 exposed cases and 18 exposed controls). The wide CI range can primarily be attributed to the low number of exposed cases, which reduces the reliability of the results to demonstrate a true association. Additionally, the study did not adjust for exposure to multiple pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and multiple myeloma using data from the 6 studies described above (Brown *et al.*, 1993; De Roos *et al*., 2005; Sorahan, 2015; Pahwa *et al*., 2012; Kachuri *et al*., 2013; Orsi *et al*., 2009). Meta-risk ratios were obtained using data from each of the 4 independent study populations, such that if a study population was already represented in the analysis by one study, then the same population analyzed by another study would not be included (e.g., Sorahan, 2015 and De Roos *et al.*, 2005 could not be used simultaneously in a meta-analysis). The combined meta-risk ratio based on data from prioritized studies (Brown *et al.*, 1993; Kachuri *et al.*, 2013; Orsi *et al.*, 2009; and Sorahan, 2015) was 1.4 (95% CI=1.0-1.9) using random-effects and fixed-effects models and the I^2 value = 0.0% indicating consistency across data sets. There was relatively no impact on the meta-risk ratio and associated 95% CI when secondary analyses were conducted using alternative estimates for a study population (e.g., substituting the data from Sorahan, 2015 for De Roos *et al.,* 2005).

(3) Hodgkin Lymphoma

In a Canadian case-control study, Karunanayake *et al.,* (2012) evaluated Hodgkin lymphoma (HL) and observed no association with glyphosate exposure following adjustment for age, province of residence, and medical history variables (OR=0.99; 95% CI=0.62-1.56; 38 cases). No adjustment was made for exposure to other pesticides.

In a hospital-based case-control study conducted by Orsi *et al*. (2009) in France, authors identified 87 HL cases and 265 age-and sex-matched controls. There was a non-statistically significant elevated odds ratio observed (OR=1.7; 95% CI=0.6–5.0; 6 exposed cases and 15 exposed controls). The wide CI range can primarily be attributed to the low number of exposed cases. Also, as noted earlier, this study did not adjust for exposure to multiple pesticides.

Chang and Delzell (2016) conducted a meta-analysis exploring glyphosate exposure and HL using data from both of these studies. A meta-risk ratio of 1.1 (95% CI=0.7-1.6) was obtained with a I^2 value of 0.0%, indicating consistency across the data sets.

HL was also evaluated in the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) and no association was observed with glyphosate use; however, the number of cases available for this analysis was limited.

(4) Non-Hodgkin Lymphoma

NHL has about 60 subtypes classified by the WHO, which may have etiological differences (Morton *et al.*, 2014). There are analyses available for particular subtypes of NHL; however, these are particularly limited by the small sample sizes. As a result, this evaluation only presents results for total NHL with the exception of the recently published analysis of the AHS cohort (Andreotti *et al.,* 2017) where sample sizes were not limited for all subtypes.

There were six studies available that investigated the association between glyphosate exposure and NHL, which was the most for any type of cancer. As discussed in Section 3.4, these studies encompass a combination of strengths and limitations. These studies are therefore discussed in more detail in this section as compared to discussions of other cancer types in order to highlight the strengths and identify the limitations for each study.

De Roos *et al*. (2005) was the only prospective cohort study available; therefore, subjects were enrolled prior to developing cancer outcomes. Disease status was determined through state cancer registries. Exposure information was obtained from a large number of licensed pesticide applicators and no proxies were used. Exposure was evaluated as ever/never use, cumulative lifetime exposure, and intensity-weighted cumulative exposure. Due to the study design, the potential for many biases were reduced. Additionally, the study adjusted and/or considered numerous factors, including use of other pesticides. Median follow-up time was approximately 7 years.; however, as discussed in Section 3.3.1, study participants provided exposure information prior to enrollment and this information was incorporated into the cumulative lifetime and intensity-weighted cumulative exposure metrics. As a result, the amount of time exposed was longer than just the follow-up time since enrollment. For applicators with the full data set, the RR for ever/never use was 1.2 (95% CI=0.7–1.9; 92 cases) with only adjustment for age. In the fully adjusted model excluding subjects with missing covariate data, the RR was similar following adjustment for age, demographic and lifestyle factors, and exposure to other pesticides (RR=1.1; 95% CI=0.7-1.9). Effect estimates obtained using cumulative lifetime exposure and intensity-weighted cumulative exposure were below 1 (RR = 0.6-0.9 when comparing to the lowest tertile). The recently published analysis of the AHS cohort with a longer follow-up

period of approximately 17.5 years (Andreotti *et al.,* 2017) also reported no association between glyphosate exposure and NHL overall or any of its subtypes.

De Roos *et al.* (2003) used pooled data from three case-controls studies evaluating NHL in white males from Nebraska, Kansas, and in Iowa and Minnesota (Cantor *et al.*, 1992; Hoar *et al.*, 1986; Zahm *et al.,* 1990; Appendix B). Exposure information was obtained from exposed individuals or their next of kin (i.e., proxy respondents) if the subjects were dead or incapacitated; however, techniques varied across the three studies. There is potential for selection bias due to exclusion of observations with missing covariate data, but only if the lack of the covariate data was associated with glyphosate exposure. The effect estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses adjusting for co-exposure to other pesticides. However, utilizing alternative hierarchical regression techniques to adjust for co-exposure to other pesticide exposures, the odds ratio was still elevated, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8).

Eriksson *et al.* (2008) is a Swedish case-control study that used detailed exposure information from exposed individuals (i.e., no use of proxy respondents), but only minimal demographic information was provided on subjects (age and sex) and a table with subject characteristics (e.g., smoking status, alcohol intake, physical activity, education) was not provided. Cases were identified through physicians and verified histopathologically. Glyphosate exposure, which was reported in 29 cases and 18 controls between 1999 and 2003, produced a statistically significant increased OR in the univariate analysis (OR=2.02; 95% CI=1.10–3.71); however, in the multivariate analysis adjustments were conducted for co-exposure to different agents including MCPA, "2,4,5-Y and/or 2,4-D", mercurial seed dressing, arsenic, creosote, and tar and the OR reduced to 1.51 (95% CI=0.77–2.94) and was not statistically significant. Additional analyses were conducted to investigate the impact of various exposure times. When exposure was for more than 10 cumulative days (the median number of days among exposed controls), the OR was 2.36 (95% CI=1.04–5.37; 17 exposed cases) and for exposure less than 10 cumulative days, the OR was 1.69 (95% CI=0.7–4.07; 12 exposed cases). By dividing the exposed cases and controls using this exposure metric, wider CIs were observed due to smaller sample sizes, which reduces the reliability of the results to demonstrate a true association. Additionally, these analyses did not account for co-exposure to other pesticides. Similarly, wider CIs were also observed when exposed cases and controls were divided by a longer exposure metric. ORs of 1.11 (95% CI=0.24-5.08) and 2.26 (95% CI=1.16-4.40) were obtained for 1-10 years and >10 years, respectively. It was not clear whether this analysis adjusted for co-exposure to other pesticides based on the statistical methods description and the subjects for each exposure group were not reported. This finding, while limited to a single study, suggests that cohort studies without sufficient follow-up time or other case-control studies which did not stratify by time since first exposure may be less sensitive in detecting risk.

Hardell *et al.* (2002) used pooled data from two case-control studies in Sweden (Hardell and Eriksson, 1999; Nordstrom *et al*., 1998; Appendix B) that examined hairy cell leukemia, a subtype of NHL, and NHL (not including hairy cell leukemia). Exposure information was collected from individuals or proxy respondents based on a working history with specific questions on exposures to different chemicals. Cases were identified from regional cancer

registries and verified histopathologically. In the univariate analysis, risk of NHL associated with glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52), but when study site, vital status, and co-exposure to other pesticides were considered in the multivariate analysis, the OR noticeably attenuated and was found to be non-statistically significant (OR=1.85; 95% CI=0.55–6.20). The wide range of the CI resulting from the small sample size (only 8 glyphosate-exposed cases and 8 glyphosate-controls).

McDuffie *et al.* (2001) is a multicenter population-based study among men of six Canadian provinces. This case-control study utilized a well-conducted exposure assessment and cases were ascertained from cancer registries or hospitals in six provinces with histopathological verification for 84% of the samples. There are concerns with control selection. There was low control participation (48%) and different sources were used for selecting controls depending on the province of residence. Effect estimates were obtained using a considerable number of exposed cases and controls (51 cases and 133 controls); however, the study did not assess co-exposure to other pesticides. There was a non-statistically significant increased risk of NHL from glyphosate exposure when adjusting for age and province (OR=1.26; 95% CI=0.87–1.80) and when adjusting for age, province and medical variables (OR=1.20; 95% CI=0.83–1.74). Medical variables found to be statistically significant included history of measles, mumps, previous cancer, skin-prick allergy tests, allergy desensitization shots, and a positive family history of cancer in a first-degree relative. It would be expected that effect estimates would attenuate if adjustment for co-exposure to other pesticides had been performed. Additional analyses were conducted to investigate differences in exposure time. When exposure was for more than 2 days/year, the OR was 2.12 (95% CI=1.20-3.73; 23 exposed cases and 36 exposed controls) compared to unexposed subjects and for exposure more than 0 and ≤ 2 days/year, the OR was 1.00 (95% CI=0.63–1.57; 28 exposed cases and 97 exposed controls) compared to unexposed subjects.

Orsi *et al.* (2009) is a French hospital-based case-control study that obtained exposure information from subjects (no proxies used) using a detailed questionnaire with lifelong residential and occupational histories followed by a discussion with a trained interviewer who was blinded to case status. No issues regarding exposure or outcome assessment were identified; however, there is potential for selection bias given the study utilized hospital-based controls (primarily from orthopedic and rhematological departments) that may not be representative of the general population that gave rise to the cases. The study evaluated several potential confounders; however, it did not assess co-exposure to other pesticides. There was no association observed between NHL and glyphosate use (OR=1.0; 95% CI=0.5-2.2; 12 exposed cases and 24 exposed controls). The low number of cases and controls exposed to glyphosate and lack of adjustment for exposure to multiple pesticides were limitations of the study.

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; De Roos *et al*., 2003; De Roos *et al*., 2005; Eriksson *et al*., 2008; and Orsi *et al*., 2009). Since the authors identified a variety of sources of heterogeneity between publications, they decided a priori to calculate meta-risk ratio estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. I^2 values were reported as a measure of inconsistency in results. For glyphosate, the meta-risk ratio was 1.5

with a 95% CI of 1.1–2.0 and the I^2 value was 32.7% indicating relatively low levels of heterogeneity among these studies. This study combined multiple smaller studies that on their own had limitations, including small sample sizes.

The 2015 IARC evaluation noted that fully adjusted effect estimates in two of the Swedish studies (Hardell *et al*., 2002 and Eriksson *et al*., 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, the IARC Working Group conducted a reexamination of the results of these studies (IARC 2015). For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65, I^2 =0%; p=0.589 for heterogeneity).

Chang and Delzell (2016) conducted their own meta-analysis exploring glyphosate exposure and NHL using six independent studies (De Roos *et al.,* 2003; De Roos *et al.,* 2005; Eriksson *et al.,* 2008; Hardell *et al.,* 2002; McDuffie *et al.,* 2001; and Orsi *et al.,* 2009). A meta-risk ratio of 1.3 (95% CI=1.0-1.6) was obtained with an I^2 value of 0.0%. In a secondary analysis, the De Roos *et al.* (2003) OR using hierarchical regression was replaced by the logistic regression OR. This change had no impact on the meta-risk ratio and associated confidence interval (meta-risk ratio=1.3; 95% CI=1.0-1.6). In another secondary analysis, the OR from McDuffie *et al.* (2001) was replaced by the OR from Hohenadel *et al.* (2011), which evaluated the same study population (minus four previously misclassified NHL cases). This analysis also yielded similar results (meta-risk ratio=1.3; 95% CI=1.0-1.7). A final analysis was performed with the replacements for both secondary analyses [i.e., logistic regression OR from De Roos *et al.* (2003) and OR from Hohenadel *et al.* (2011)]. The results were relatively the same as the other meta-analyses (meta-risk ratio=1.4; 95% CI=1.0-1.8). Chang and Delzell (2016) also tested for publication bias using Egger's linear regression approach to evaluating funnel plot asymmetry, and found no significant asymmetry indicating little evidence of publication bias; however, given the small sample size (n=6), this analysis would lack power and the results are not considered meaningful.

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.

Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI)[a]	Covariate Adjustments in Analyses
Leukemia					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.0 (0.5-1.9)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	 1.0 1.9 (0.8-4.5) 1.0 (0.4-2.9)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	 1.0 1.9 (0.8-4.7) 0.7 (0.2-2.1)	Age, demographic and lifestyle factors, and other pesticides[b]
Brown *et al.* (1990)	Case-Control	USA: Iowa and Minnesota	Ever/never	0.9 (0.5-1.6)	Vital status, age, tobacco use, family history of lymphopoietic cancer, high occupations, and high risk exposures
Multiple Myeloma					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	2.6 (0.7-9.4)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	 1.0 1.1 (0.4-3.5) 1.9 (0.6-6.3)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	 1.0 1.2 (0.4-3.8) 2.1 (0.6-7.0)	Age, demographic and lifestyle factors, and other pesticides[b]
Brown *et al.* (1993)	Case-Control	USA: Iowa	Ever/never	1.7 (0.8-3.6)	Age and vital status
Kachuri *et al.* (2013) (extended analysis of Pahwa 2012)	Case-Control	Canada	Ever/never	1.19 (0.76-1.87)	Age, province of residence, smoking status, selected medical conditions, family history of cancer, and use of a proxy respondent
			Days per year of use: 0 to ≤2 days/year >2 days/year	 0.72 (0.39-1.32) 2.04 (0.98-4.23)	Age, province of residence, smoking status, selected medical conditions, family history of cancer, and use of a proxy respondent
Pahwa *et al.* (2012)	Case-Control	Canada	Ever/never	1.22 (0.77-1.93)	Age group, province of residence, and statistically significant medical history variables

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.

Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI)[a]	Covariate Adjustments in Analyses
Orsi *et al.* (2009)	Case-Control	France	Ever/never	2.4 (0.8-7.3)	Age, centre, and socioeconomic category
Sorahan (2015) Reanalysis of De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.12 (0.5-2.49)	Age and sex
				1.24 (0.52-2.94)	Age sex, lifestyle factors, and other pesticides
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009)	Nested Case-Control	USA: Iowa and North Carolina	Ever/never	0.5 (0.2-1.0)	Age and education
Hodgkin Lymphoma (HL)					
Karunanayake *et al.* (2012)	Case-Control	Canada	Ever/never	0.99 (0.62-1.56)	Age group, province of residence, and statistically significant medical history variables
Orsi *et al.* (2009)	Case-Control	France	Ever/never	1.7 (0.6-5.0)	Age, centre, and socioeconomic category
Non-Hodgkin Lymphoma (NHL)					
De Roos *et al.* (2005)	Prospective Cohort	USA: Iowa and North Carolina	Ever/never	1.1 (0.7-1.9)	Age, demographic and lifestyle factors, and other pesticides[b]
			Cumulative Exposure Days (by tertile cut points): 1-20 21-56 57-2,678	 1.0 0.7 (0.4-1.4) 0.9 (0.5-1.6)	Age, demographic and lifestyle factors, and other pesticides[b]
			Intensity-Weighted Cumulative Exposure Days (by tertile cut points): 0.1-79.5 79.6-337.1 337.2-18,241	 1.0 0.6 (0.3-1.1) 0.8 (0.5-1.4)	Age, demographic and lifestyle factors, and other pesticides[b]
De Roos *et al.* (2003)	Case-Control	USA: Iowa, Nebraska, Minnesota, and Kansas	Ever/never	1.6 (0.9-2.8)	Age, study site, and use of other pesticides
Eriksson *et al.* (2008)	Case-Control	Sweden	Ever/never	Multivariate: 1.51 (0.77-2.94)	Age, sex, year of diagnosis or enrollment, and exposure to other pesticides
			Days per year of use: ≤ 10 days >10 days	 1.69 (0.70-4.07) 2.36 (1.04-5.37)	Age, sex, and year of diagnosis or enrollment
			Years of use: 1-10 years >10 years	 1.11 (0.24-5.08) 2.26 (1.16-4.40)	Unknown

Table 3.4. Summary of Findings: Non-Solid Tumor Cancer Studies.

Study	Study Design	Study Location	Exposure Metric	Adjusted Effect Estimate: RR or OR (95% CI)[a]	Covariate Adjustments in Analyses
Hardell *et al.* (2002)	Case-Control	Sweden	Ever/never	Multivariate: 1.85 (0.55-6.20)	Study, study area, vital status, and exposure to other pesticides
McDuffie *et al.* (2001)	Case-Control	Canada	Ever/never	1.20 (0.83-1.74)	Age, province of residence, and statistically significant medical variables
			Days per year of use: >0 and ≤ 2 days >2 days	 1.00 (0.63-1.57) 2.12 (1.20 -3.73)	Age and province of residence
Orsi *et al.* (2009)	Case-Control	France	Ever/never	1.0 (0.5-2.2)	Age, centre, and socioeconomic category

[a] Some studies report multiple quantitative risk measurements. This table reports the most highly adjusted quantitative measurements.
[b] De Roos *et al.* (2005) excluded subjects missing covariate data for demographic and lifestyle factors and exposure to other pesticides; therefore, the number of subjects included in each analysis varies.

3.6 Discussion

A total of 63 individual studies were identified in the systematic review. The data from 7 of these studies were used in pooled analyses by other studies; therefore, they were not subjected to detailed evaluation. Overall, 3 studies, 19 studies, and 34 studies were assigned high, moderate, or low rankings, respectively. All of the high and moderate quality studies were considered informative with regard to the carcinogenic potential of glyphosate. Additionally, the recently published analysis of the AHS cohort (Andreotti *et al.*, 2017) was also considered as part of this evaluation.

There was no evidence of an association between glyphosate exposure and solid tumors, leukemia, or HL. These conclusions are consistent with those recently conducted by IARC, EFSA, and JMPR who also concluded there is no evidence of an association for these tumors at this time. The data should be considered limited though with only one or two studies available for almost all of the cancer types investigated. The remainder of this discussion focuses on multiple myeloma and NHL. Study elements for the available studies and their potential to impact effect estimates are examined; however, the discussion is applicable in most cases to all of the epidemiological studies used in this evaluation.

Multiple Myeloma

Four studies were available evaluating the association between glyphosate exposure and risk of multiple myeloma in the initial evaluation presented to the SAP in December 2016 (Brown *et al*., 1993; De Roos *et al*., 2005; Orsi *et al*., 2009; Pahwa *et al*., 2012). Since that time, a recent analysis of the AHS cohort has been published (Andreotti *et al.*, 2017), which included evaluation of multiple myeloma. One reanalysis (Sorahan, 2015) and one extended analysis (Kachuri *et al*., 2013) were also included in the evaluation. The effect estimates for ever/never use ranged from 1.19 to 2.6 although none were found to be statistically significant. Only one study (De Roos *et al*., 2005) adjusted for co-exposures to other pesticides; therefore, potential confounding was not addressed in the other studies. There was an indication of a possible exposure-response relationship; however, this was the only study that evaluated the exposure-response relationship for multiple myeloma. Reanalysis of the full dataset by Sorahan (2015) raised concerns about whether the restricted dataset used for these analyses was representative of the whole cohort. Furthermore, in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017) with a longer follow-up period and almost 5 times more exposed cases, there was no evidence of an association between glyphosate exposure and risk of multiple myeloma. There was a single study of MGUS, a precursor to multiple myeloma, which showed decreased risk with exposure to glyphosate; however, the study did not adjust for exposure to other pesticides. Overall, the available evidence does not link glyphosate exposure to multiple myeloma.

NHL

Six studies were available evaluating the association between glyphosate exposure and risk of NHL in the initial evaluation presented to the SAP in December 2016. Since that time, a recent analysis of the AHS cohort has been published (Andreotti *et al.*, 2017), which included evaluation of NHL. Effect estimates for ever/never use ranged from 1.0-1.85 in adjusted

analyses with none reaching statistical significance (Figure 3.2). Two of these studies did not adjust for co-exposures to other pesticides (McDuffie *et al*., 2001; Orsi *et al*., 2009). Many of the evaluated studies were limited by small sample sizes, which resulted in large confidence intervals and reduced the reliability of the results to demonstrate a true association. Meta-analyses were performed by IARC (2015) and Chang and Delzell (2016) using these results for the ever/never use metric. Both analyses reported similar meta-risk ratios ranging from 1.3-1.5, depending on the effect estimates and studies included in the analyses. Any of the meta-analysis estimates that were statistically significant were all borderline with the lower limit of the 95% CI just slightly over 1. For example, the lower 95% confidence limit reported by IARC (2015) was 1.03 and the lower 95% confidence limit displayed in Figure 3.2 generated by the agency is 1.01. It should also be noted that publication bias may play a role in this evaluation given there is a tendency to only publish positive results and potential concerns regarding glyphosate have only been raised in recent years.

With respect to meta-analyses, caution should be taken when interpreting results. Meta-analyses are a systematic way to combine data from several studies to estimate a summary effect. Analyses were performed with 6 studies, which many would consider small for performing meta-analyses. Rarely will meta-analyses synthesize data from studies with identical study designs and methods. In the meta-analyses performed by IARC (2015) and Chang and Delzell (2016), inclusion was primarily based on whether a study addressed the broader question regarding the association between glyphosate exposure and risk of NHL. For meaningful results, careful consideration of whether studies are similar and should be combined in the analysis. Furthermore, the bias and confounding issues inherent for each individual study are carried over into the meta-analyses. Across the NHL studies, study characteristics varied, such as overall study design (i.e., cohort and case-control), source population, proxy respondent use, covariate adjustments, and confounding control. Even if these differences are not detected statistically, the meta-analysis estimate should be considered in the context of the data that are used to generate it.

Using cumulative lifetime and intensity-weighted cumulative exposure metrics, all effect estimates were less than 1 (OR = 0.6-0.9 when comparing to the lowest tertile) in the AHS cohort study (De Roos *et al.*, 2005). Similar results were obtained in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017). Two case-control studies (Eriksson *et al*., 2008; McDuffie *et al*., 2001) evaluated the association of glyphosate exposure and NHL stratifying exposure by days per year of use. These studies obtained effect estimates greater than 1, which conflicted with the results in the prospective cohort study; however, these estimates from the case-control studies do not appear to be adjusted for co-exposures to other pesticides. By dividing the total number of exposed cases and controls by these exposure metrics in Eriksson *et al*. (2008), wider confidence intervals were observed due to small sample sizes, which reduces the reliability of the results to demonstrate a true association. Furthermore, as mentioned previously (and will be discussed further below), there was clearly strong potential for confounding from exposure to other pesticides. In each instance where a study adjusted for co-exposure to other pesticides, the adjusted effect estimate decreased in magnitude, including other analyses performed in one of these case-control studies. Consequently, lack of adjustment for co-exposure to other pesticides in these analyses could partially explain the conflicting results between the cohort and case-control studies.

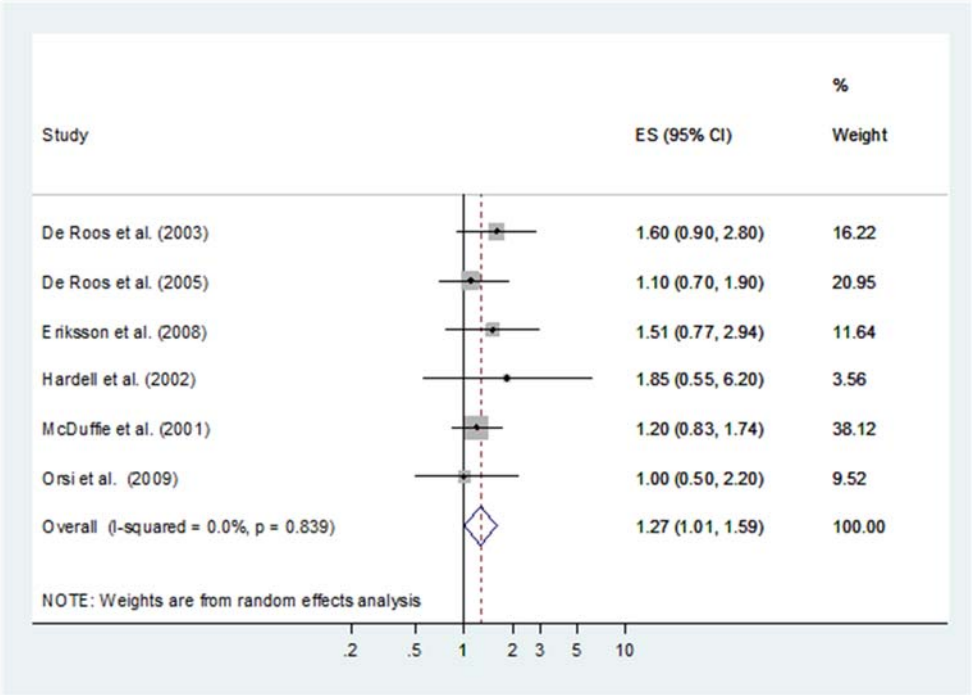

Figure 3.2. Forest plot of effect estimates (denoted as ES for effect sizes) and associated 95% confidence intervals (CI) for non-Hodgkin lymphoma (NHL).

The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Control for confounding varied considerably across studies (Table 3.2). Studies primarily adjusted for standard variables, such as age, gender, and residency location. Co-exposure to other pesticides was considered for several of the NHL studies for ever/never use (De Roos *et al.*, 2003; De Roos *et al.*, 2005; Eriksson *et al.,* 2008; Hardell *et al.*, 2002); however, analyses of exposure-response and latency effects did not appear to adjust for these co-exposures. The recent analysis by Andreotti *et al*. (2017) also adjusted for co-exposure to other pesticides.

There is clearly a strong potential for confounding by co-exposures to other pesticides since many are highly correlated and have been reported to be risk factors for NHL. In the studies that did report a quantitative measure adjusted for the use of other pesticides, the risk was always found to be closer to the null than the risk calculated prior to this adjustment. For examples, Eriksson *et al*. (2008) reported unadjusted and adjusted effect estimates of 2.02 (95% CI: 1.10-3.71) and 1.51 (95% CI: 0.77-2.94), respectively. Comparing the magnitude of those effect sizes on the natural log scale, the unadjusted effect was β=0.70 (95% CI: 0.10, 1.31) while the adjusted effect was β=0.41 (95% CI: -0.26, 1.08), suggesting a difference compatible with a degree of confounding by those herbicide co-exposures which appeared to have inflated the unadjusted effect upwards by 70% on the natural log scale (or by 46% on the OR scale). This demonstrates the profound effect this adjustment has on effect estimates and the concern for residual confounding by other pesticides that cause NHL themselves. As discussed in Section 3.2.4, other potential confounders have also been identified. With an association between glyphosate exposure and the outcome of interest, occupational exposure to diesel exhaust fumes, solvents, livestock and other farm animals, and UV radiation are highly likely confounders in the

NHL studies; however, none of the studies accounted for these potential confounders. These confounders and/or other unknown factors could explain the increased risk of NHL among farmers, particularly since increased risk of NHL to farmers has been previously documented and existed prior to the introduction of glyphosate.

Recall bias and missing data are also limitations in most of the studies. In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain discrepancies in study findings. During their lifetime, farmers are typically exposed to multiple pesticides and often several may be used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, the results can be subject to misclassification and recall bias.

Furthermore, the use of proxy respondents has the potential to increase recall bias and thus may increase exposure misclassification, especially for proxy respondents not directly involved in farming operations that may be more prone to inaccurate responses than directly interviewed subjects. In some of the NHL studies, the study participants were interviewed directly to assess exposure (De Roos *et al.*, 2005; Eriksson *et al.*, 2008; McDuffie *et al.*, 2001; Orsi *et al.*, 2009), making proxy respondent use a non-issue for these studies. In other studies, however, study participants or proxy respondents were interviewed to assess exposure (Hardell *et al.*, 2002, De Roos *et al.*, 2003). De Roos *et al.* (2003) did not find type of respondent to be statistically significant, but Hardell *et al.* (2002) did not conduct analyses to evaluate the impact of proxy use. In non-NHL studies, proxy analyses were conducted in a small subset (Kachuri *et al.*, 2013; Lee *et al.,* 2004b; Lee *et al.,* 2005; Yiin *et al.*, 2012) and differences in effect estimates were often observed. In a few studies, respondent type was used as an adjustment variable when calculating effect estimates (Band *et al.*, 2011; Kachuri *et al.,* 2013; Lee *et al.*, 2005). As with all study design elements of case-control studies, one concern is whether or not the use of proxy respondents had a differential impact on the cases and controls included in the study because any differential impact may result in differential exposure misclassification. When use of proxy respondents was comparable for cases and controls in the full study population, it could be assumed that there is less concern for potential recall bias from the use of proxy respondents. In Hardell *et al.,* (2002), the percentage of cases and controls with proxy respondents was not fully reported for cases and controls though and this adds a potential source of uncertainty for the study. Moreover, when proxy respondents were used in a study, the percentages were usually reported only for the full study population and were not reported for the specific cases and controls exposed to glyphosate. This lack of information makes it difficult to assess the degree to which recall bias may have occurred due to the use of proxy respondents.

Previously, some have argued that the follow-up period (median = 7 years) in De Roos *et al.* (2005) is not sufficiently long to account for the latency of NHL (Portier *et al.*, 2016); however, an analysis of the AHS cohort was recently published (Andreotti *et al.*, 2017) with an extended

follow-up of 17.5 years. This study reported no association between glyphosate exposure and all lymphohematopoietic cancers, NHL, or any of its subtypes across exposure metrics. No association was observed in unlagged or lagged analyses, after adjustment for pesticides linked to NHL in previous AHS analyses, and after exclusion of multiple myeloma from the NHL grouping.

It was also noted that reference groups differed across studies. For example, some studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; and Eriksson *et al*., 2008) eliminated cases and controls who had been exposed to certain classes of pesticides, which may have resulted in selection bias and/or recall bias that may ultimately impact the effect estimates obtained in these studies. In the dose-response analysis by De Roos *et al*. (2005), the lowest exposed tertile was used as the reference group in an effort to reduce the potential for residual confounding by unmeasured covariates due to lack of comparability observed between the never exposed group and the higher exposed groups. Analyses were also performed using the unexposed group as the reference. This study consistently found no evidence of an association between glyphosate exposure and NHL using different exposure metrics and reference groups. Similarly, there was no evidence of an association observed in the recent analysis of the AHS cohort (Andreotti *et al.*, 2017) with a longer follow-up period.

There are conflicting views on how to interpret the overall results for NHL. Some believe that the data are indicative of a potential association between glyphosate exposure and risk of NHL. This is primarily based on reported effect estimates across case-control studies and the associated meta-analyses greater than 1. Additionally, the analysis conducted by Eriksson *et al*. (2008) observed a slightly statistically significant increase for those with more than 10 years of exposure prior to diagnosis. There were also two case-control studies that investigated the association of glyphosate exposure and NHL by stratifying exposure by days per year of use that reported effect estimates greater than 1 for groups with the highest exposure.

Conversely, others have viewed the effect estimates as relatively small in magnitude and observed associations could be explained by chance and/or bias, particularly since studies have reported farmers develop NHL at excess rates and this risk existed prior to the introduction of glyphosate. All of the effect estimates for ever/never use were non-statistically significant. Several studies reported effect estimates approximately equal to the null. The widest confidence intervals were observed for the highest effect estimates indicating these effect estimate are less reliable. Sample sizes were limited in several of these case-control studies. Meta-analyses were based on studies with varying study characteristics. Given the limitations and concerns discussed above for the individual studies included in this evaluation, chance and/or bias cannot be excluded as an explanation for the relatively small increase observed in the meta-risk ratios. Meanwhile, analyses performed by De Roos *et al.* (2005) and Andreotti *et al*. (2017) reported effect estimates less than 1 for cumulative lifetime exposure and intensity-weighted cumulative exposure and these extensive analyses did not detect any exposure-response relationship, which conflicts with the two case-control studies that indicate potential for an exposure-response relationship comparing two groups stratified by days per year of use. Although increased effect estimates were observed in one case-control study (Eriksson *et al*., 2008) for subjects exposed more than 10 years prior to diagnosis and in two case-control studies (McDuffie *et al*., 2001; Eriksson *et al*., 2008) that stratified exposure by days per year of use, none of these analyses

appeared to adjust for exposures to other pesticides, which has been found to be particularly important for these analyses and would be expected to attenuate these estimates towards the null. Furthermore, none of the studies in this evaluation of glyphosate exposure and risk of NHL accounted for other potential confounders, such as diesel exhaust fumes, solvents, animals, and UV radiation.

Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. The agency will continue to monitor the literature for studies and any updates to the AHS will be considered when available.

4.0 Data Evaluation of Animal Carcinogenicity Studies

4.1 Introduction

Cancer bioassays in animals have historically been the primary studies available to evaluate cancer hazard in humans since, until recently, epidemiological evidence was limited. The results of these bioassays, as well as results from screening assays for genotoxicity, are considered in a weight-of-evidence approach to determine the potential of a chemical to induce cancer in humans. Carcinogenicity studies in two rodent species are required for the registration of food use pesticides or when the use of a pesticide is likely to result in repeated human exposure over a considerable portion of the human lifespan (40 CFR Part 158.500). Rodent carcinogenicity studies identified from the data collection phase of the systematic review were evaluated for study quality and acceptable studies were evaluated in the context of the 2005 EPA Guidelines for Carcinogen Risk Assessment as described in Sections 4.2 and 4.3 below, respectively. This included studies using glyphosate salts, which dissociate quickly in aqueous environments to the glyphosate acid and the corresponding cation. The cations would not be expected to impact the toxicity results compared to studies where animals are treated with glyphosate acid alone.

4.2 Consideration of Study Quality for Animal Carcinogenicity Studies

The agency has published test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200) and combined chronic/carcinogenicity studies (OCSPP 870.4300) in rodents which have been harmonized with OECD guidelines (Test Nos. 451 and 453). Test substances are typically administered in animal carcinogenicity studies by the oral route for food use pesticides. The studies are generally conducted in mice and rats with exposure durations of 18-24 months for mice and 24 months for rats, which represent exposures of the majority of the expected lifespan in these animals. Guideline carcinogenicity studies are designed to test three or more doses in both sexes (with at least 50 animals/sex/dose) with adequate dose spacing to characterize tumor dose-response relationships. Key considerations when evaluating carcinogenicity studies for cancer hazard assessment include identification of target organs of carcinogenicity, increased incidence of tumors or proportion of malignant neoplasms, and reduction in the time to appearance of tumors relative to the concurrent control group (OECD TG 451).

There are a number of criteria the agency uses when evaluating the technical adequacy of animal carcinogenicity studies. A primary criterion is the determination of the adequacy of dosing. The 2005 EPA Guidelines for Carcinogen Risk Assessment recommends that the highest dose level selected should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors; or without inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms); however, the high dose need not exceed 1,000 mg/kg/day (i.e., limit dose) (OCSPP 870.4200; OCSPP 870.4300). Additional criteria to judge the technical adequacy and acceptability of animal carcinogenicity studies are provided in the test guidelines as well as other published sources (NTP, 1984; OSTP, 1985; Chhabra *et al*., 1990). As stated in the 2005 EPA Guidelines for Carcinogen Risk Assessment, studies that are judged to be wholly inadequate in protocol, conduct or results, should be discarded from

analysis. Studies the agency consider acceptable are further evaluated for potential tumor effects.

Following study quality evaluation, a total of 8 chronic/carcinogenicity studies in the rat and 6 carcinogenicity studies in the mouse were considered acceptable for use in the current evaluation for the active ingredient glyphosate and were subsequently evaluated in the context of the 2005 EPA Guidelines for Carcinogen Risk Assessment as described in Section 4.3. A number of studies were judged to be inadequate in protocol, conduct or reporting and were not considered in the analysis of glyphosate. These studies and the justification for not including them in the analysis are listed below:

1. A two-year chronic oral toxicity study in Albino rats by Reyna (1974)[13]. The study was considered inadequate to assess carcinogenicity due to insufficient reporting on the histopathology findings in the control and treatment groups. Approximately 70 animals were unaccounted for across the study.

2. A two-year drinking water study in Wistar rats with a formulated product (13.6% ammonium salt) by Chruscielska *et al.*, (2000). In addition to deficiencies including inadequate reporting of water consumption and body weight data, this study was conducted with a glyphosate formulated product and not the active ingredient glyphosate, which is the focus of this review. Glyphosate formulations contain various components other than glyphosate and it has been hypothesized these components are more toxic than glyphosate alone. The agency is collaborating with NTP to systematically investigate the mechanism(s) of toxicity for glyphosate and glyphosate formulations. This project is discussed in more detail in Section 7.0 of this document.

3. An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) on the skin. Study deficiencies included small number (20) of animals, tested only males, and lack of histopathological examination.

4. A carcinogenicity study in Swiss albino mice (Kumar, 2001)[14]. This study was not included due to the presence of a viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all dose groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al*., 2012). Murine leukemia viruses (MuLVs) are also a common cause of lymphoma in many different strains of mice (Ward, 2006). For example, Tadesse-Heath *et al*. (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice infected with MuLVs. Although the lymphoma incidences in Kumar (2001) were within or near normal background variation, it is not clear whether or not the viral infection may have contributed to the lymphoma incidence reported or the lower survival seen at the high dose in this study.

[13] MRID 00062507.
[14] MRID 49987403. In Greim *et al.* (2015), the same study is cited as Feinchemie Schwebda (2001).

5. A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included. The agency does not have access to this study to perform an independent assessment of its conduct and; however, Greim *et al*. (2015) stated that the study "is considered unreliable for carcinogenicity evaluation" and there were "several deviations from the OECD Test Guideline 453".

4.3 Assessment of Animal Carcinogenicity Studies

The agency considers many factors when interpreting the results of carcinogenicity studies. The 2005 EPA Guidelines for Carcinogen Risk Assessment are intended as a guidance only and does not provide a checklist for determining whether tumor findings are related to treatment. These guidelines emphasize the importance of weighing multiple lines of evidence in reaching conclusions regarding human carcinogenic potential of chemicals. Evaluation of observed tumor findings takes into consideration both biological and statistical significance. There are several factors in the 2005 EPA Guidelines for Carcinogen Risk Assessment used in the weight-of-evidence evaluation of individual studies. For this evaluation, the interpretation of the evidence related to tumor findings is described below.

Dose Selection

Doses should be selected based on relevant toxicological information. Caution is taken in administering an excessively high dose that would confound the interpretation of the results to humans. As mentioned above, the 2005 EPA Guidelines for Carcinogen Risk Assessment recommends that the highest dose level selected should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors; or without inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms); however, the high dose is not recommended to exceed 1,000 mg/kg/day (OCSPP 870.4200; OCSPP 870.4300). Doses should provide relevant dose-response data for evaluating human hazard for human health risk assessment. In the case of glyphosate, the low (oral) systemic toxicity and limited pharmacokinetic (PK) data for this chemical make it difficult to define a maximum tolerated dose (MTD) for the cancer bioassays. A large number of the carcinogenicity studies conducted with glyphosate approach or exceed the limit dose. The 2005 EPA Guidelines for Carcinogen Risk Assessment state that "weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed". As such, the agency puts less weight on observations of increased incidence of tumors that only occur near or above the limit dose.

Statistical analyses to evaluate dose response and tumor incidences

The main aim of statistical evaluation is to determine whether exposure to the test agent is associated with an increase in tumor development, rather than due to chance alone. Tumors were selected for statistical analyses in the current evaluation if the study report identified tumors as statistically significant and/or have been identified by the reviewer as potentially biologically significant based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls. For toxicological studies submitted to the agency for pesticide registration, including animal carcinogenicity studies, detailed reviews are performed, which summarize study findings and identify effects, such as tumors, for evaluation.

Statistical analyses should be performed on each tumor type separately. The incidence of benign and malignant lesions of the same cell type, usually within a single tissue or organ, are considered separately, but may be combined when scientifically defensible (McConnell *et al*., 1986). Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. The 2005 Guidelines for Carcinogen Risk Assessment states that:

"A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

In the current evaluation, animals sacrificed for interim evaluations or died prior to the interim sacrifices were not included in the statistical evaluations to avoid dilution of a potential carcinogenic effect. Additionally, survival was evaluated across dose groups and no significant mortality differences were observed in any of the studies. As a result, there was no need to incorporate survival adjustments into the analyses (e.g., Peto prevalence test). The Cochran-Armitage Test for Trend (Snedecor and Cochran, 1967; one-sided) was used for trend analysis. For pairwise comparisons, the Fisher Exact Test (Fisher, 1950; one-sided) was used to determine if incidences observed in treated groups were different from concurrent controls. Furthermore, the 2005 EPA Guidelines for Carcinogen Risk Assessment state that "considerations of multiple comparisons should also be taken into account". Multiple comparison methods control the familywise error rate, such that the probability of Type I error (incorrect rejection of the null hypothesis or "false positive") for the pairwise comparisons in the family does not exceed the alpha level. In the current evaluation, the Benjamini-Hochberg correction method was used to adjust for multiple comparisons (Benjamini and Hochberg, 1995).

For the current evaluation, statistical significance observed in either test is judged in the context of all of the available evidence. Statistically significant responses may or may not be biologically significant and vice versa (Hsu and Stedeford, 2010; EPA, 2005). If a trend was found to be statistically significant, a closer examination of the tumor incidence was taken to determine whether the data demonstrate a monotonic dose-response where an increase in tumor incidence is expected with corresponding increase in dose. Therefore, statistically significant results with fluctuating tumor incidence across doses are not weighed as heavily as those displaying a monotonic dose-response. If a pair-wise comparison was found to be statistically significant, a closer examination of the tumor incidence and other lines of evidence was taken to determine whether the response was biologically significant. Factors considered in determining the biological relevance of a response are discussed below.

All statistical analyses were reanalyzed for the purposes of this evaluation to ensure consistent methods were applied (M. Perron; 12-DEC-2017; TXR#0057690).

Historical Control Data
As indicated in the 2005 EPA Guidelines for Carcinogen Risk Assessment (Section 2.2.2.1.3), the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals. Additional insight into the statistical and/or biological significance of a response can come from the consideration of historical control data (Tarone, 1982; Haseman, 1995; EPA, 2005). Historical control data can add to the analysis, particularly by enabling identification of uncommon tumor types or high spontaneous incidence of a tumor in a given animal strain. Generally speaking, statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average.

Historical control data are also useful to determine if concurrent control tumor incidences are consistent with previously reported tumor rates (Haseman, 1995). Historical control data available to the agency from the performing laboratory for the same species and strain for a study were considered in the current evaluation. These data were primarily generated within 3 years and in limited cases within 5 years of the study date. Given the large number of age-related tumor outcomes in long-term rodent bioassays, and thus the large number of potential statistical tests run, caution is taken when interpreting results that have marginal statistical significance or in which incidence rates in concurrent controls are unusually low in comparison with historical controls since there may be an artificial inflation of the differences between concurrent controls and treated groups. Consequently, in the current evaluation, unusually low incidence in concurrent controls was noted when applicable and considered as part of the weight-of-evidence for the tumor findings. Identification of common or uncommon situations prompts further thought about the meaning of the response in the current study in context with other observations in animal studies and with other evidence about the carcinogenic potential of the agent.

Evidence of supporting preneoplastic lesions or related non-neoplastic lesions
Carcinogenicity rodent studies are designed to examine the production of tumors as well as preneoplastic lesions and other indications of chronic toxicity that may provide evidence of treatment-related effects and insights into the way the test agent produces tumors (EPA, 2005). As such, the presence or lack of supporting preneoplastic or other related non-neoplastic changes were noted in the current evaluation of each study and considered in the weight-of-evidence to aid in the determination of biological significance since these lesions would not be expected for age-related tumors in carcinogenicity with continuous treatment. In the current evaluation, the agency investigated lesions in organs where tumors were observed and demonstrated biological significance based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls.

Additional Considerations
Other observations can strengthen or lessen the significance of tumor findings in carcinogenicity studies. Such factors include: uncommon tumor types; tumors at multiple sites; tumors in multiple species, strains, or both sexes; progression of lesions from preneoplastic to benign to malignant; reduced latency of neoplastic lesions (i.e., time to tumor); presence of metastases; unusual magnitude of tumor response; and proportion of malignant tumors (EPA, 2005). The

agency considers all of the above factors when determining the significance of tumor findings in animal carcinogenicity studies.

4.4 Summary of Animal Carcinogenicity Studies

A total of 8 chronic toxicity/carcinogenicity studies in the rat[15] and 6 carcinogenicity studies in the mouse were considered acceptable and evaluated in the weight-of-evidence analysis for glyphosate. This includes all of the studies that were part of the 2015 CARC evaluation plus an additional 4 studies identified from the systematic review. In the 2015 CARC evaluation, for some of the studies considered, the CARC relied on summary data that was provided in the supplement to the Greim *et al*. (2015) review article. Due to the ongoing data collection effort and the acquiring of studies not previously submitted, the agency no longer needs to rely on the Greim *et al*. (2015) review article for the study data generated in relevant studies, allowing for a more complete and independent analysis. It should be noted that studies have been cited differently in this evaluation as compared to Greim *et al*. (2015) so these alternative citations have been noted for applicable studies.

The carcinogenicity studies conducted in the rat and mouse that were considered for the analysis are discussed in Sections 4.5 and 4.6, respectively. In these sections, short study summaries are presented which include information on the study design (including test material, strain of animal used, and doses and route of administration) as well as study findings including effects on survival, general toxicity observed, relevant non-neoplastic lesions, and the incidence and characterization of any tumor findings. The characterization of the tumor response(s) is based on the considerations previously discussed in Section 4.3 for interpreting the significance of tumor findings in animal carcinogenicity studies. The rat and mouse carcinogenicity studies are all summarized in Table 4.11 and Table 4.18, respectively.

4.5 Rat Carcinogenicity Studies with Glyphosate

4.5.1 Lankas, 1981 (MRID 00093879)[16]

In a chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at dietary doses of 0, 3/3, 10/11, and 31/34 mg/kg/day (M/F) for 26 months.

There were no treatment-related effects on survival at any dose level. The highest dose tested of approximately 31 mg/kg/day was not considered a maximum tolerable dose to assess the carcinogenic potential of glyphosate. Consequently, a second study (Stout and Ruecker, 1990) was conducted at higher doses, which is summarized in the Section 4.5.3.

A statistically significant trend was reported for the testicular interstitial tumors; however, closer examination of the tumor incidence indicates that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose. The

[15] Note: the original draft of this Issue Paper included 9 studies in rats; however, one study (Burnett, 1979) was removed since the study was conducted with a contaminant of glyphosate, not the active ingredient glyphosate.
[16] In Greim *et al.* (2015), the same study is cited as Monsanto (1981).

incidence at the high dose was found to be statistically significant as compared to the concurrent controls (raw and adjusted p-values).

Table 4.1. Testicular Interstitial Cell Tumors in Male Sprague-Dawley Rats (Lankas, 1981) Cochran-Armitage Trend Test & Fisher's Exact Test Results.

	0 mg/kg/day	3.05 mg/kg/day	10.3 mg/kg/day	31.49 mg/kg/day
Incidence	0/47[a]	3/49	1/47	6/50
(%)	(0)	(6)	(2)	(12)
Raw p-value =	0.011**	0.129	0.500	0.016*
Adjusted p-value =	0.032*	0.172	0.500	0.032*

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01.
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

The study report provided historical control information for 5 studies of similar duration (24-29 months) run concurrently within 9 months of the termination of the study in the same laboratory. The historical control range for this tumor type was 3.4%-6.7% (mean = 4.5%) when considering all animals. When only considering animals that survived to terminal sacrifice, the historical control range was 6.2%-27.3% (mean = 9.6%). These data indicate that the incidence of testicular cell tumors in concurrent controls (0%) appears to be unusually low for this tumor type. Furthermore, the incidence at all doses, including the high dose, was within the historical control range when evaluating animals at terminal sacrifice. There were no supporting preneoplastic or other related non-neoplastic changes observed.

4.5.2 Stout and Ruecker, 1990 (MRID 41643801)[17]

In a chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary doses of 0, 89/113, 362/457 or 940/1183 mg/kg/day M/F) for 24 months. The highest dose tested in this study approaches or exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Tumor findings at these high doses are given less weight.

There was no significant increase in mortality. Three types of tumors were evaluated in this study: pancreatic cell adenomas, hepatocellular adenomas, and thyroid C-cell adenomas in males. A discussion of each tumor type by organ is presented below:

1. Pancreas: Tumor incidences of pancreatic islet cell tumors in male rats are presented in Tables 4.2. The incidence of pancreatic islet cell tumors lacked monotonic dose-responses and trend analyses were not statistically significant. There was also no statistical significance of the pairwise comparisons. Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range for the adenomas was 1.8%-8.3% (mean = 5.3%). These data are presented in Table 4.3 and indicate that the incidence of adenomas in concurrent controls (2%) was at the lower limit

[17] In Greim *et al.* (2015), the same study is cited as Monsanto (1990).

of the historical range. There were no supporting preneoplastic or other related non-neoplastic changes observed and no evidence of progression from adenomas to carcinomas.

Table 4.2. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990) Cochran-Armitage Trend Test & Fisher's Exact Test Results.

Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma				
Incidence	1/43[a]	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
Raw p-value =	0.176	0.018*	0.135	0.042*
Adjusted p-value =	0.176	0.071	0.176	0.083
Carcinoma				
Incidence	1/43[c]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
Raw p-value =	-[d]	-[d]	-[d]	-[d]
Adjusted p-value =	-[d]	-[d]	-[d]	-[d]
Combined				
Incidence	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
Raw p-value =	0.242	0.052	0.275	0.108
Adjusted p-value =	0.275	0.209	0.275	0.215

Note: Trend test results denoted at control; * denotes significance at p=0.05.

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).

b. First adenoma in the study was observed at week 81 in the 940 mg/kg/day group.

c. First carcinoma in the study was observed at week 105 in the controls.

d. Trend p-value not reported since tumor incidence decreased with increasing dose.

Table 4.3. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague- Dawley Rats (MRID No. 41728701).

Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59	-
Percentage (%)	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%	5.3%

2. Liver: Tumor incidences of liver tumors in male rats are presented in Tables 4.4. There was a statistically significant dose trend for liver adenomas; however, the trend was not statistically significant with an adjustment for multiple comparisons. Closer examination of the incidence indicates a relatively flat response at the low- and mid-dose with only an increase observed at the high-dose (940 mg/kg/day); however, the incidence of liver adenomas at the high-dose was not statistically significant when compared to the concurrent controls (raw or adjusted p-values). Carcinomas and combined adenomas/carcinomas lacked statistical significance in trend and pairwise comparisons (Table 4.4). Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range was 1.4%-18.3% (mean = 9.2%) for the adenomas and 0%-6.7% for carcinomas (mean = 2.6%). These data are provided in Table 4.5 and indicate that the observed incidences at all dose levels were within the historical control ranges. Except for a single animal at the mid-dose late in the study (89

weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were observed. Furthermore, there was no evidence of progression from adenomas to carcinomas.

Table 4.4. Hepatocellular Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990) Cochran-Armitage Trend Test & Fisher's Exact Test Results

Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma Incidence (%) Raw p-value = Adjusted p-value =	2/44[a] (5) 0.022* 0.089	2/45 (4) 0.700 0.700	3/49 (6) 0.551 0.700	7/48[b] (15) 0.101 0.202
Carcinoma Incidence (%) Raw p-value = Adjusted p-value =	3/44 (7) -[d] -[d]	2/45 (4) -[d] -[d]	1/49 (2) -[d] -[d]	2/48[c] (4) -[d] -[d]
Combined Incidence (%) Raw p-value = Adjusted p-value =	5/44 (11) 0.078 0.312	4/45 (9) 0.769 0.808	4/49 (8) 0.808 0.808	9/48 (19) 0.245 0.489

Note: Trend test results denoted at control; * denotes significance at p=0.05.

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).

b. First adenoma in the study was observed at week 88 in the 940 mg/kg/day group.

c. First carcinoma in the study was observed at week 85 in the 940 mg/kg/day group.

d. Trend p-value not reported since tumor incidence decreased with increasing dose.

Table 4.5. Historical Control Data — Hepatocellular Tumors in Male Sprague- Dawley Rats (MRID No. 41728701).

Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Adenomas								
Tumor Incidence	5/60	11/68	1/70	3/59	11/60	5/60	4/60	-
Percentage (%)	8.3%	16.2%	1.4%	5.1%	18.3%	8.3%	6.7%	9.2%
Carcinomas								
Tumor Incidence	4/60	0/68	1/70	2/59	3/60	1/60	0/60	-
Percentage (%)	6.7%	0%	1.4%	3.4%	5%	1.7%	0%	2.6%

3. Thyroid: Tumor incidences of thyroid tumors in male and female rats are presented in Tables 4.6 and 4.7, respectively. For males, no statistically significant trends were observed for adenomas, carcinomas, or combined adenomas/carcinomas. For females, a statistically significant trend was observed for adenomas and combined adenomas/carcinomas; however, the trend was not statistically significant with adjustment for multiple comparisons. There was no statistical significance in pairwise analyses. Historical control data were provided for 7 studies conducted in the same laboratory from 1983-1989 (within 1-4 years of when Stout and Ruecker (1990) was performed). The historical control range was 3.3%-10% (mean = 6.1%) for the adenomas and 0%-2.9% for carcinomas (mean = 0.9%). These data are provided in Table 4.8.

Non-neoplastic lesions (thyroid C-cell hyperplasia) were observed; however, there was a lack of a monotonic dose-response for these histopathological findings and no dose-related increase in severity to support tumor findings (Table 4.9). There was also no evidence of progression from adenomas to carcinomas.

Table 4.6. Thyroid C-Cell Tumors in Male Sprague-Dawley Rats (Stout and Ruecker, 1990)
Cochran-Armitage Trend Test & Fisher's Exact Test Results

Tumor Type	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Adenoma				
Incidence	2/54[a, b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
Raw p-value =	0.079	0.348	0.060	0.099
Adjusted p-value =	0.132	0.348	0.132	0.132
Carcinoma				
Incidence	0/54	2/55[c]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
Raw p-value =	0.457	0.252	1.000	0.518
Adjusted p-value =	0.518	0.518	1.000	0.518
Combined				
Incidence	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
Raw p-value =	0.087	0.141	0.060	0.060
Adjusted p-value =	0.116	0.141	0.116	0.116

Note: Trend test results denoted at control.
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
b. First adenoma in the study was observed at week 54 in the controls.
c. First carcinoma in the study was observed at week 93 in the 89 mg/kg/day group.

Table 4.7. Thyroid C-Cell Tumors in Female Sprague Dawley Rats
Cochran-Armitage Trend Test & Fisher's Exact Test Results (Stout and Ruecker, 1990).

Tumor Type	0 mg/kg/day	113 mg/kg/day	457 mg/kg/day	1183 mg/kg/day
Adenoma				
Incidence	2/57[a]	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
Raw p-value =	0.040*	0.710	0.147	0.124
Adjusted p-value =	0.159	0.710	0.196	0.196
Carcinoma				
Incidence	0/57	0/60	1/59[c]	0/55
(%)	(0)	(0)	(2)	(0)
Raw p-value =	0.494	1.000	0.509	1.000
Adjusted p-value =	0.509	1.000	0.509	1.000
Adenoma/Carcinoma				
Incidence	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
Raw p-value =	0.042*	0.710	0.090	0.124
Adjusted p-value =	0.166	0.710	0.166	0.166

Note: Trend test results denoted at control; * denotes significant at p=0.05.
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55 (interim sacrifice).
b. First adenoma in the study was observed at week 72 in the controls.
c. First carcinoma in the study was observed at week 93 in the 457 mg/kg/day group.

Table 4.8. Historical Control Data — Thyroid C-Cell Tumors in Female Sprague- Dawley Rats (MRID No. 41728701).								
Study No.	1	2	3	4	5	6	7	Mean
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89	-
Adenomas								
Tumor Incidence	2/60	3/69	7/70	3/59	5/59	5/60	2/60	-
Percentage (%)	3.3%	4.3%	10.0%	5.1%	8.5%	8.3%	3.3%	6.1%
Carcinomas								
Tumor Incidence	1/60	2/69	0/70	1/59	0/59	0/60	0/60	-
Percentage (%)	1.7%	2.9%	0%	1.7%	0%	0%	0%	0.9%

Table 4.9. Thyroid Non-Neoplastic Lesions (Stout and Ruecker, 1990)				
Males				
Dose	0 mg/kg/day	89 mg/kg/day	362 mg/kg/day	940 mg/kg/day
Total Incidences of thyroid C-cell hyperplasia and severity scores	5/60 (8%) Diffuse (moderate) – 1 Multi-focal (minimal) – 3 Focal (mild) – 1	1/60 (2%) Focal (mild) – 1	6/60 (10%) Focal (minimal) – 4 Multi-focal (minimal) – 1 Multi-Focal (mild) – 1	5/60 (8%) Focal (minimal) – 2 Focal (mild) – 1 Multi-focal (mild) – 1 Multi-focal (moderate) – 1
Females				
	0 mg/kg/day	113 mg/kg/day	457 mg/kg/day	1183 mg/kg/day
Thyroid C-cell hyperplasia and severity scores	10/60 (17%) Diffuse (moderate) – 1 Focal (mild) – 1 Focal (minimal) – 1 Focal (mild) – 1 Focal (moderate) – 1 Multi-focal (minimal) – 3 Multi-focal (moderate) – 1 Diffuse (moderate) – 1	5/60 (8%) Focal (mild) – 3 Focal (minimal) – 1 Multi-focal (minimal) – 1	9/60 (15%) Focal (minimal) – 4 Multi-focal (minimal) – 2 Multi-focal (mild) – 3	5/60 (8%) Focal (mild) – 1 Focal (minimal) – 1 Multi-focal (mild) – 2 Diffuse (moderate) – 1

*Data taken from pages 1071-2114 of the study report.

4.5.3 Atkinson *et al.*, 1993a (MRID 49631701)[18]

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 Sprague-Dawley rats/sex/dose in the diet at doses of 0, 11/12, 112/109, 320/347, and 1147/1134 mg/kg/day for 104 weeks (M/F) for 104 weeks. An additional 35 rats/sex/dose were included for 1-year interim sacrifice.

[18] Note: In Greim *et al.* (2015), the same study is cited as Cheminova (1993a).

No adverse effects on survival were seen in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidences in the study.

4.5.4 Brammer, 2001 (MRID 49704601)[19]

In a combined chronic toxicity/carcinogenicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 rats/sex received diets containing doses of 0, 121/145, 361/437 or 1214/1498 mg/kg/day for 24 months, in males/females, respectively. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

A statistically significant higher survival (p=0.02) was observed in males at the highest dose tested at the end of 104 weeks relative to concurrent controls, and a statistically significant trend for improved survival was observed in treated males (p=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low-, mid-, and high-dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low-, mid- and high-dose groups, respectively. There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested. As shown in Table 4.10, a statistically significant trend in the incidences of liver adenomas was observed in male rats; however, a monotonic dose-response was not observed upon closer examination of the incidence data. Tumor incidences appear to fluctuate with increases observed at the low- and high-dose and no tumors observed in the control and mid-dose. Statistical significance with raw (unadjusted) p-values was observed for the tumor incidence at the high-dose (1214 mg/kg/day) when compared to concurrent controls; however, it was not statistically significant with an adjustment for multiple comparisons (p= 0.055). The improved survival in the high-dose group may help explain a modestly higher incidence of an age-related background tumor like liver adenomas and this corresponds with the lack of associated lesions observed in the study.

Table 4.10. Liver Adenomas in Male Wistar Rats (Brammer, 2001)
Cochran-Armitage Trend Test and Fisher's Exact Test Results.

	0 mg/kg/day	121 mg/kg/day	361 mg/kg/day	1214 mg/kg/day
Adenoma Incidence (%)	0/44[a] (0)	2/48 (4)	0/48 (0)	5/49 (10)
Raw p-value =	0.010*	0.269	1.000	0.037*
Adjusted p-value =	0.029*	0.269	1.000	0.055

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

4.5.5 Pavkov and Wyand 1987 (MRIDs 40214007, 41209905, 41209907)

Glyphosate trimesium salt (sulfosate, 56.2% pure) was tested in a 2-year chronic feeding/carcinogenicity study in male and female Sprague-Dawley (Crl:CD[SD]BR) rats. Sixty

[19] Note: In Greim *et al.* (2015), the same study is cited as Syngenta (2001).

animals/sex were tested in control group 1 (basal diet, no vehicle), 80/sex were tested in control group 2 (basal diet plus propylene g1ycol at 1% w/w vehicle) and in the low and mid-dose groups, and 90/sex were tested in the high dose group. The following dose levels were tested: 0, 4.2/5.4, 21.2/27 or 41.8/55.7 mg/kg/day in males and females respectively.

Treatment had no effect on survival. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidences in the study.

4.5.6 Suresh, 1996 (MRID 49987401)[20]

In a combined chronic toxicity/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 6.3/8.6, 59.4/88.5, and 595.2/886 mg/kg/day glyphosate for 24 months in males and females respectively. The highest dose tested in females in this study approaches the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

No adverse effects on survival were observed in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.5.7 Enemoto, 1997 (MRID 50017103-50017105)[21]

In a combined chronic toxicity and carcinogenicity study, groups of 50 Sprague-Dawley rats/sex/group received daily dietary doses of 0, 104/115, 354/393 and 1127/1247 mg/kg bw/day glyphosate for males and females, respectively. In addition, 10 rats/sex/group were included for interim sacrifices at 26, 52, and 78 weeks. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

There were no changes in mortality at any of the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.5.8 Wood *et al.*, 2009a (MRID 49957404)[22]

In a combined chronic toxicity/carcinogenicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 95.0, 316.9, and 1229.7 mg/kg/day glyphosate for males and female, respectively. The highest dose tested in this study exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

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[20] Note: In Greim *et al.* (2015), the same study is cited as Feinchemie Schwebda (1996).
[21] Note: In Greim *et al.* (2015), the same study is cited as Arysta Life Sciences (1997b).
[22] Note: In Greim *et al.* (2015), the same study is cited as NuFarm (2009b).

No adverse effects on survival were seen in either sex across the doses tested. There were no treatment-related preneoplastic or related non-neoplastic lesions in either sex at any dose level.

In female rats, mammary gland tumors were noted. Tumor incidences for mammary gland adenomas, adenocarcinomas, and combined adenomas/adenocarcinomas in female mice are presented in Table 4.11. Statistically significant trends were observed for the adenocarcinoma and combined analyses; however, statistical significance was only seen for the combined analyses following adjustment for multiple comparisons. There was no statistical significance observed in pairwise comparisons.

Table 4.11 Mammary Gland Tumor Incidences in Female Rats (Wood *et al.*, 2009a) Fisher's Exact Test and Cochran-Armitage Trend Test Results

Tumor Type	0 mg/kg/day	95.0 mg/kg/day	316.9 mg/kg/day	1229.7 mg/kg/day
Adenoma Incidence (%) Raw p-value = Adjusted p-value =	0/48[a] (0) 0.062 0.124	0/51 (0) 1.000 1.000	0/50 (0) 1.000 1.000	2/50 (4) 0.258 0.258
Adenocarcinoma Incidence (%) Raw p-value = Adjusted p-value =	2/48 (4) 0.043* 0.172	3/51 (6) 0.529 0.705	1/50 (2) 0.886 0.886	6/50 (12) 0.148 0.296
Combined Incidence (%) Raw p-value = Adjusted p-value =	2/48 (4) 0.007** 0.028*	3/51 (6) 0.529 0.705	1/50 (2) 0.886 0.886	8/50 (16) 0.053 0.105

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significant at p=0.01.
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

4.5.9 Summary of Rat Data

In 4 of the 8 rat studies conducted with glyphosate, no tumors were identified for evaluation. Of the remaining 4 rat studies, a statistically significant trend was observed for tumor incidences in the testes, liver, or mammary gland following adjustment for multiple comparisons. A statistically significant pairwise comparison was only observed following adjustment for multiple comparisons for testicular tumors at the highest dose tested (31 mg/kg/day) in one individual study. In some cases, the tumor incidence across doses did not demonstrate a monotonic dose response. There was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions or evidence of tumor progression (progression from pre-neoplastic to malignancy) to support biological significance of tumor findings. In a limited number of cases, the agency considered historical control data to inform the relevance of a tumor increase, which indicated concurrent controls were unusually low or the observed incidences were within the historical control range in most instances.

Table 4.12. Summary of Rat Carcinogenicity Studies			
Study	**Dose Range**	**Pre-Neoplastic or Related Non-Neoplastic Lesions**	**Tumors Incidences, Statistical Significance, and Related Comments**
Lankas (1981) Sprague-Dawley rats	98.7% Technical in diet 0, 3/3, 10/11, and 31/34 mg/kg/day [M/F]	None observed	Statistically significant trend observed for testicular interstitial cell tumors; however, did not observe monotonic dose-response with higher incidence at low-dose than mid-dose. Incidences were 0/47 in controls, 3/49 at low-dose, 1/47 at mid-dose, and 6/50 at high-dose. Increased incidence at high-dose statistically significant, but unusually low control incidence (based on terminal sacrifice historical control data in study report) inflated increase at high-dose.
Stout and Ruecker (1990) Sprague-Dawley rats	96.5% Technical in diet 0, 89/113, 362/457 and 940/1183 mg/kg/day [M/F] for 24 months	None observed	Pancreatic tumors lacked statistically significant trend. Tumor incidence for pancreatic adenomas in males were 1/43 in controls, 8/45 at the low-dose, 5/49 at the mid-dose, and 7/48 at the high-dose. Concurrent control incidence for this tumor type was at the lower bound of the historical control range for performing laboratory. Negative trend observed for carcinomas. Combined adenoma/carcinoma incidence similar except low-dose was 2/43. No statistically significant pairwise comparisons, including the highest dose tested which is approaching/exceeding 1,000 mg/kg/day. No statistically significant trends or pairwise comparisons for hepatocellular tumors following adjustment for multiple comparisons. Negative trend observed for carcinomas. The highest dose tested approached/exceeded 1,000 mg/kg/day. All incidences within historical control range for performing laboratory. No statistically significant trend for thyroid C-cell tumors in males. For females, statistically significant trend for combined adenomas/carcinomas following adjustment for multiple comparisons. Incidences for combined adenomas/carcinomas were 2/57 in controls, 2/60 at the low-dose, 7/59 at the mid-dose, and 6/55 at the high-dose. No statistically significant pairwise comparisons, including the highest dose tested which is approaching/exceeding 1,000 mg/kg/day.
Atkinson *et al.* (1993a) Sprague-Dawley rats	98.9% Technical in diet 0, 11/12, 112/109, 320/347, and 1147/1134 mg/kg/day for 104 weeks (M/F)	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.

Table 4.12. Summary of Rat Carcinogenicity Studies			
Study	**Dose Range**	**Pre-Neoplastic or Related Non-Neoplastic Lesions**	**Tumors Incidences, Statistical Significance, and Related Comments**
Brammer (2001) Wistar rats	97.6% Technical in diet 0, 121/145, 361/437 and 1214/1498 mg/kg/day [M/F]	None observed	Statistically significant trend in liver adenomas in males. Non-monotonic dose-response with incidences at 0/44 in controls, 2/48 at the low-dose, 0/48 at the mid-dose, and 5/49 at the high-dose. No statistically significant pairwise comparisons following adjustment for multiple comparisons, including the highest dose tested which exceeded 1,000 mg/kg/day.
Pavkov and Wyand (1987) Sprague-Dawley rats	56.2% Technical (Trimesium salt; Sulfosate) 0, 4.2/5.4, 21.2/27 and 41.8/55.7 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation.
Suresh (1996) Wistar rats	96.0-96.8% Technical in diet 0, 6.3/8.6, 59.4/88.5, and 595.2/886 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.
Enemoto (1997) Sprague-Dawley rats	94.61-97.56% Technical in diet 0, 104/115, 354/393 and 1127/1247 mg/kg/day [M/F]	None observed	There were no tumors identified for evaluation, including the highest dose tested which exceeded 1,000 mg/kg/day.
Wood *et al.* (2009a) Wistar rats	95.7% Technical in diet 0, 86/105, 285/349 or 1077/1382 mg/kg/day [M/F]	None observed	Statistically significant trends were observed for the combined mammary gland adenoma/adenocarcinoma analyses following adjustment for multiple comparisons. Incidences were 2/48 in controls, 3/51 at the low-dose, 1/50 at the mid-dose, and 8/50 at the high-dose. No statistically significant pairwise comparisons, including the highest dose tested which exceed 1,000 mg/kg/day.

4.6 Mouse Carcinogenicity Studies with Glyphosate

4.6.1 Reyna and Gordon, 1973 (MRID 00061113)

In an 18-month carcinogenicity study, groups of 50 Swiss white mice/sex/dose were fed glyphosate at dietary levels of approximately 17 mg/kg/day and 50 mg/kg/day. There was no effect on survival at any of the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study. Although only ten mice/sex/dose were examined for histopathological changes, there were no statistically significant increases in tumors observed in the study; therefore, this deficiency would not impact the overall conclusion regarding tumor findings.

4.6.2 Knezevich and Hogan, 1983 (MRID 00130406)[23]

Groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary doses of 0, 161/195, 835/968, 4945/6069 mg/kg/day for males and females, respectively for 24 months. The highest dose tested in this study far exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Furthermore, the mid-dose tested in this study was approaching 1,000 mg/kg/day. Tumor findings at these high doses are given less weight. No effect on survival was observed. A low incidence of renal tubule adenomas, which are considered rare, were noted in males. The incidences of renal tubule adenomas following initial evaluation of the study were reported as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR# 0004370). In 1985, the registrant directed a re-evaluation of the original renal sections by a consulting pathologist. This re-evaluation identified a small renal tubule adenoma in one control male mouse, which was not diagnosed as such in the original pathology report. In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related.

Subsequently, the agency requested a Pathology Work Group (PWG) evaluate the kidney sections. The PWG examined all sections of the kidney, including the additional renal sections, and were blinded to treatment group. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 4.13 with results from statistical analyses. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it is appropriate to combine the incidences from these two tumor types for purposes of evaluation and statistical analysis. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the concurrent controls and there was no evidence of a statistically significant linear trend; 3) multiple renal tumors were not found in any

[23] Note: In Greim *et al.* (2015), the same study is cited as Monsanto (1983).

animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study (TXR# 0005590).

Table 4.13. Renal Tubular Cell Tumors in Male CD-1 Mice (Knezevich and Hogan, 1983) Cochran-Armitage Trend Test & Fisher's Exact Test Results.

Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenoma Incidence (%) Raw p-value = Adjusted p-value =	1/49 (2) 0.442 1.000	0/49 (0) 1.000 1.000	0/50 (0) 1.000 1.000	1/50 (2) 0.758 1.000
Carcinoma Incidence (%) Raw p-value = Adjusted p-value =	0/49 (0) 0.063 0.190	0/49 (0) 1.000 1.000	1/50 (2) 0.505 0.505	2/50 (4) 0.253 0.379
Combined Incidence (%) Raw p-value = Adjusted p-value =	1/49 (2) 0.065 0.259	0/49 (0) 1.000 1.000	1/50 (2) 0.758 1.000	3/50 (6) 0.316 0.633

Note: Trend test results denoted at control.

Historical control data from 14 studies conducted between 1977 and 1981 (within <1 to 3 years of when Knezevich and Hogan (1983) was performed) at the performing laboratory (Table 4.14) indicated that the mouse renal tubular adenomas ranged from 0 to 3.3% and the incidence in the current study was within the historical control range (TXR# 0007252).

Table 4.14. Historical Control Data- Kidney tumors in CD-1 Mice (TXR #0007252).

Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77- 4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma	0	1	0	0	0	0	0	0	0	2	0	0	0	0

Histopathological examinations noted chronic interstitial nephritis and tubular epithelial changes (basophilia and hypertrophy) in the kidneys of male rats in the study (Table 4.15). The increased incidence of chronic interstitial nephritis in males lacked a dose-response. The incidence in controls of bilateral interstitial nephritis was higher than low-dose group and approximately the same as the mid-dose group. Unilateral chronic interstitial nephritis was only seen in 1 animal in the low- and high-dose groups. Furthermore, chronic interstitial nephritis is not considered to be a precursor lesion for tubular neoplasms. A monotonic dose-response was not observed for the epithelial basophilia and hypertrophy, such that the incidence fluctuated with dose and the lowest incidence was observed at the highest dose tested. There was no increase in supporting preneoplastic or related non-neoplastic renal tubular lesions (e.g., tubular epithelial necrosis/regeneration, hyperplasia) observed in male mice.

Table 4.15. Kidney Histopathological Alterations in Male CD-1 Mice (Knezevich and Hogan, 1983)				
Males				
Dose	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Bilateral Chronic Interstitial Nephritis	5/49 (10%)	1/49 (2%)	7/50 (14%)	11/50 (22%)
Unilateral Chronic Interstitial Nephritis	0/49 (0%)	1/49 (2%)	0/49 (0%)	1/50 (2%)
Proximal Tubule Epithelial Basophilia and Hypertrophy	15/49 (31%)	10/49 (20%)	15/50 (30%)	7/50 (14%)

*Data taken from page 305 and 306, and the study pathology report; incidences were moderate diffuse

4.6.3 Atkinson, 1993b (MRID 49631702)[24]

In a carcinogenicity study, glyphosate (>97% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet for 104 weeks at doses of 0, 98/102, 297/298, 988/1000 mg/kg/day for males and females, respectively. No interim sacrifices were performed.

There was no effect on survival in the study. There were no preneoplastic lesions or related non-neoplastic lesions observed. As shown in Table 4.16, hemangiosarcomas were found in 4/45 (9%) of high-dose male mice (1000 mg/kg/day) compared to none in the concurrent controls or other treated groups. Hemangiosarcomas are commonly observed in mice (generally more common in males for CD-1 strain) as both spontaneous and treatment-related tumors arising from endothelial cells. As vascular tumors, they can occur at different sites, with liver and spleen tending to be the most common sites in mice. In the high-dose mice with hemangiosarcomas, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. A statistically significant trend was observed. Closer examination of the incidence indicates a relatively flat response at the low- and mid-dose with only an increase observed at the high-dose; however, the incidence of hemangiosarcomas at the high-dose was not statistically significant when compared to the concurrent controls.

Table 4.16. Hemangiosarcomas in Male CD-1 Mice (Atkinson, 1993b) Cochran-Armitage Trend Test and Fisher's Exact Test Results.				
Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcoma Incidence (%)	0/47[a] (0)	0/46 (0)	0/50 (0)	4/45 (9)
Raw p-value =	0.003**	1.000	1.000	0.053
Adjusted p-value =	0.006**	1.000	1.000	0.053

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.

[24] Note: In Greim *et al.* (2015), the same study is cited as Cheminova (1993b).

4.6.4 Wood *et al.*, 2009b (MRID 49957402)[25]

In a feeding study, CD-1 mice (50/sex/dose) received glyphosate (95.7%) for 80 weeks at dietary dose levels of 0, 71.4/97.9, 234.2/299.5, or 810/1081.2 mg/kg/day for males and females, respectively. The highest dose tested in this study approaches or exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300).

There was no effect on survival in the study. In male mice at the high dose, there were increases in the incidences of lung adenocarcinomas and malignant lymphomas. A discussion of each tumor type is presented below:

1. Lung: Tumor incidence for lung adenomas, adenocarcinomas, and combined adenomas/adenocarcinomas are presented in Table 4.17. A statistically significant trend was only noted for the adenocarcinomas; however, the trend was not statistically significant with adjustment for multiple comparisons. Closer examination of the tumor incidence indicates the dose-response was relatively flat at the low- and mid-dose with only an increase observed at the high-dose and the incidence of lung adenocarcinomas at the high-dose (810 mg/kg/day) was not statistically significant when compared to the concurrent controls. There were no treatment-related preneoplastic or related non-neoplastic lesions observed.

2. Malignant lymphoma: Tumor incidence for malignant lymphoma are also presented in Table 4.18. A statistically significant trend was observed and the incidence at the high-dose (810 mg/kg/day) was statistically significantly elevated as compared to concurrent controls with the raw (unadjusted) p-value; however, with an adjustment for multiple comparisons, the increased incidence at the high-dose was not statistically significant (p= 0.059). Historical control data have been submitted (MRIDs 50464501and 50464601) from the same testing laboratory for 10 studies of similar duration. These data were generated within approximately 5 years of the Wood *et al.* (2009b) study. The historical control range was 0%-32% (mean = 8.7%). All observed incidences of this tumor type were within the historical control range.

[25] Note: In Greim et al. (2015), the same study is cited as NuFarm (2009a).

Table 4.17. Lung Tumors in Male CD-1 Mice (Wood *et al.*, 2009b) Fisher's Exact Test and Cochran-Armitage Trend Test Results.				
Dose (mg/kg/day)	0	71.4	234.2	810
Lung Adenoma Incidence (%)	9/44 (20)	7/46 (15)	9/48 (19)	4/45 (9)
Raw p-value =	-[b]	-[b]	-[b]	-[b]
Adjusted p-value =	-[b]	-[b]	-[b]	-[b]
Lung Adenocarcinoma (%)	5/44[a] (11)	5/46 (11)	7/48 (15)	11/45 (24)
Raw p-value =	0.026*	0.659	0.443	0.091
Adjusted p-value =	0.103	0.659	0.590	0.182
Lung Combined Incidence (%)	14/44 (32)	12/46 (26)	16/48 (33)	15/45 (33)
Raw p-value =	0.328	0.797	0.527	0.529
Adjusted p-value =	0.706	0.797	0.706	0.706

Note: Trend test results denoted at control; * denotes significance at p=0.05;** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).
b = Trend and pairwise p-values not reported since tumor incidence decreased with increasing dose.

Table 4.18. Malignant Lymphomas in Male CD-1 Mice (Wood *et al.*, 2009b) Fisher's Exact Test and Cochran-Armitage Trend Test Results.				
Dose (mg/kg/day)	0	71.4	234.2	810
Malignant Lymphoma Incidence (%)	0/44 (0)	1/46 (2)	2/48 (4)	5/45 (11)
Raw p-value =	0.006**	0.511	0.269	0.029*
Adjusted p-value =	0.025*	0.511	0.359	0.059

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).

4.6.5 Sugimoto, 1997 (MRID 50017108 - 50017109)[26]

In a carcinogenicity study, glyphosate (purity 97.56 and 94.61%; two lots) was administered to groups of 50 male and 50 female Specific-Pathogen-Free (SPF) ICR (Crj: CD-1) mice/dose in the diet at dose levels of 0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg/day for males and females, respectively, for 18 months. The highest dose tested in this study far exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300). Furthermore, the mid-dose tested in this study was approaching 1,000 mg/kg/day. Tumor findings at these high doses are given less weight.

[26]Note: In Greim et al. (2015), the same study is cited as Arysta Life Sciences (1997b)

There were no treatment-related effects on mortality or survival. There were no changes in histopathological findings observed.

Hemangiomas in female mice were found to occur at different sites. The tumor incidences are presented in Table 4.19. A statistically significant trend was observed. Tumor incidence at the high-dose, which was approximately 4 times the recommended high-dose in test guidelines (4116 mg/kg/day), was statistically significant as compared to concurrent controls.

Table 4.19. Hemangioma Incidences (Sugimoto, 1997)
Fisher's Exact Test and Cochran-Armitage Trend Test Results

Tumor Type	0 mg/kg/day	153.2 mg/kg/day	786.8 mg/kg/day	4116 mg/kg/day
Hemangioma Incidence (%) Raw p-value = Adjusted p-value =	0/48 (0) 0.002** 0.005**	0/47 (0) 1.000 1.000	2/45 (4) 0.231 0.231	5/45 (11) 0.024* 0.035*

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01.
a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52 (interim sacrifice).

4.6.6 Pavkov and Turnier, 1987 (MRIDs 40214006, 41209907)

Glyphosate trimesium salt (sulfosate, 56.2% pure) was tested in a 2-year chronic feeding/carcinogenicity study in male and female CD-1 mice. Sixty animals/sex were tested in control group 1 (basal diet, no vehicle), 80/sex were tested in control group 2 (basal diet plus propylene glycol at 1% w/w vehicle) and in the low- and mid-dose groups, and 90/sex were tested in the high-dose group. The following dose levels were tested: 0, 11.7/16, 118/159, and 991/1341 mg/kg/day for males and females, respectively.

No adverse effects on survival were seen in either sex across the doses tested. There were no changes in histopathological findings observed. There were no treatment-related increases in tumor incidence observed in the study.

4.6.7 Summary of Mouse Data

No tumors were identified for evaluation in 2 of the 6 mouse carcinogenicity studies. In the remaining 4 mouse studies, 3 observed a statistically significant trend in tumor incidences in the hemangiosarcomas, malignant lymphomas, or hemangiomas following adjustment for multiple comparisons. In one individual study, a statistically significant pairwise comparison was only observed following adjustment for multiple comparisons for hemangiomas at the highest dose tested, which was more than 4X the limit dose. There was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions or evidence of tumor progression (progression from pre-neoplastic to malignancy) to support biological significance of tumor findings. In a limited number of cases, historical control data were available which the observed tumor incidences were within the historical control range.

Table 4.20. Summary of Mouse Carcinogenicity Studies			
Study	**Dose Range**	**Pre-Neoplastic or Related Non-Neoplastic Lesions**	**Tumors Incidences, Statistical Significance, and Related Comments**
Reyna and Gordon (1973) Swiss white mice	0, 17 or 50 mg/kg/day for 18 months	None observed	There were no tumors identified for evaluation.
Knezevich and Hogan (1983) CD-1 mice	99.78% Technical in diet 0, 161/195, 835/968, 4945/6069 mg/kg/day for [M/F] for 24 months.	Chronic interstitial nephritis lacked dose-response and not considered relevant to renal tumors. Tubular epithelial changes in kidney were approximately the same in controls, low- and mid-doses and then decreased at high-dose.	No statistical significance in trend or pairwise comparisons, including the mid- and high-doses which approached or exceeded 1,000 mg/kg/day. Incidence of adenomas within historical control range for performing laboratory.
Atkinson *et al.* (1993b). CD-1 mice	97.5 - 100.2% Technical in diet 0, 98/102, 297/298, 988/1000 mg/kg/day for 104 weeks (M/F)	None observed	Statistically significant trend for hemangiosarcomas that were only observed in 4/45 (9%) high-dose male mice. Increased incidence was not statistically significant from the concurrent controls at all doses, including the highest dose tested which is approximately 1,000 mg/kg/day.
Wood *et al.* (2009b) CD-1 mice	95.7% Technical in diet 0, 71.4/97.9, 234.2/299.5, or 810/1081.2 mg/kg/day [M/F] for 80 weeks	None observed	No statistically significance in trend or pairwise comparisons following adjustment for multiple comparisons. Negative trend observed for adenomas. Statistically significant trend for malignant lymphoma with incidences of 0/44 in controls, 1/46 at the low-dose, 2/48 at the mid-dose, and 5/45 at the high-dose. No statistically significant pairwise results following adjustment for multiple comparisons, including the highest dose tested which was approaching 1,000 mg/kg/day. All observed incidences within historical control range for performing laboratory.

Table 4.20. Summary of Mouse Carcinogenicity Studies			
Study	**Dose Range**	**Pre-Neoplastic or Related Non-Neoplastic Lesions**	**Tumors Incidences, Statistical Significance, and Related Comments**
Sugimoto (1997) CD-1 mice	94.61 – 97.56% Technical in diet 0, 165/153.2, 838.1/786.8, or 4348/4116 mg/kg/day [M/F] for 18 months	None observed	Statistically significant trend for hemangiomas in female mice following adjustment for multiple comparisons with incidences of 0/48 in controls, 0/47 at the low-dose, 2/45 at the mid-dose, and 5/45 at the high-dose. Increased incidence at high-dose statistically significant following adjustment for multiple comparisons. Highest dose tested was more than 4X the limit dose.
Pavkov and Turnier (1987) CD-1 mice	56.2% Technical (Trimesium salt; Sulfosate) 0, 11.7/16, 118/159, and 991/1341 mg/kg/day [M/F] for 24 months.	None observed	There were no tumors identified for evaluation, including the highest dose tested which approached/exceeded 1,000 mg/kg/day.

4.7 Absorption, Distribution, Metabolism, Excretion (ADME)

The 2005 EPA Guidelines for Carcinogen Risk Assessment also permit analysis of other key data that may provide valuable insights into the likelihood of human cancer risk from exposure to a chemical, such as information regarding the absorption, distribution, metabolism, and excretion (ADME) of a test chemical. EPA's Harmonized Test Guidelines for pesticides include a series of studies for characterizing a chemical's metabolism and pharmacokinetics. As described in the test guideline (OCSPP 870.7485), testing of the disposition of a test substance is designed to obtain adequate information on its: absorption, distribution, biotransformation (metabolism), and excretion, which can all collectively aid in understanding the chemical's mechanism of toxicity. Basic pharmacokinetic/toxicokinetic parameters determined from these studies can also provide information on the potential for accumulation of the test substance in tissues and/or organs and the potential for induction of biotransformation as a result of exposure to the test substance. These data can be used to assess the adequacy and relevance of the extrapolation of animal toxicity data (particularly chronic toxicity and/or carcinogenicity data) to estimate human risk.

Oral exposure is considered the primary route of concern for glyphosate. The maximum absorption from the GI tract for glyphosate was estimated to be ~30% with one study showing up to 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.

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 (NTP, 1992), 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.

In general, EPA and OECD guideline ADME studies are designed for a different purpose and do not provide the information needed to adequately determine whether linear kinetics is still occurring at high doses of glyphosate. These studies are often limited to one or two doses and do not include time course data. A well-conducted pharmacokinetic study testing multiple doses is needed to conclusively make this determination.

4.8 Discussion

Glyphosate has been extensively tested in rodents to evaluate its carcinogenic potential. A total of 14 rodent carcinogenicity studies were considered to be adequate for this analysis. Eight studies were conducted in the rat and 6 studies were conducted in the mouse. When a potential tumor signal was identified in a study, the agency considered several factors. Consistent with the EPA's 2005 Guidelines for Carcinogen Risk Assessment, the agency evaluated the tumor responses for both statistical and biological significance by considering factors such as historical control data; rarity of tumor types; tumors at multiple sites; tumors in multiple species, strains, or both sexes; progression of lesions from preneoplastic to benign to malignant; reduced latency of neoplastic lesions (i.e., time to tumor); presence of metastases; unusual magnitude of tumor response; proportion of malignant tumors; and dose-related increases. When these factors were considered together, the agency made a determination of whether or not the observed tumor was related to treatment with glyphosate. A weight of the evidence approach was used to determine the carcinogenic potential of glyphosate in rodents.

In 4 of the 8 rat studies conducted with glyphosate, no tumors were identified for evaluation. Of the remaining 4 rat studies, tumor incidences were evaluated in detail for testicular, pancreatic, hepatocellular, thyroid C-cell, and mammary gland tumors. In 2 of the 6 mouse studies, no tumors were identified for evaluation. In the remaining 4 mouse studies, tumor incidences were evaluated in detail for hemangiosarcomas, malignant lymphoma, hemangiomas, lung, and kidney tumors. Below are the weight of evidence evaluations for each tumor type.

Testicular Tumors

In Table 4.1, a statistically significant trend was observed for testicular interstitial cell tumors (adjusted p-value = 0.032) and pairwise significance was observed at the highest dose tested of 31 mg/kg/day (adjusted p-value = 0.032) in male Sprague-Dawley rats (Lankas, 1981). Closer examination of the tumor incidence indicated that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. It was also noted that the incidence of testicular cell tumors in concurrent controls (0%) appears to be unusually low for this tumor type as compared to historical controls from the performing laboratory. These data also indicated that the incidence at the highest dose tested was outside the historical control range when all animals were considered, but within the terminal historical control range for the performing laboratory. Testicular interstitial cell tumors are relatively common in Sprague-Dawley rats and this tumor type is difficult to distinguish from simple hyperplasia. Testicular tumors were not seen in the other 7 rat studies, many of which tested up to or beyond the limit dose (1000 mg/kg/day). More specifically, of the 4 other studies performed in Sprague-Dawley rats (Stout and Ruecker, 1990; Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997), 3 were tested at doses 30X higher or more than the highest dose tested in Lankas (1981) and no testicular tumors were observed. Furthermore, there were no testicular tumors observed in the 6 mouse bioassays.

Pancreatic Tumors

In Table 4.2, no statistically significant trends were observed for pancreatic islet cell tumors in male Sprague-Dawley rats (Stout and Ruecker, 1990). Raw p-values were statistically

significant for adenomas at the low and high dose for pairwise comparisons; however, these were not statistically significant following adjustment for multiple comparisons. Closer examination of the tumor incidence indicated that the data do not demonstrate a monotonic dose response with greater incidence observed at the low-dose as compared at the mid-dose and high-dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Historical control data from the performing laboratory for pancreatic adenomas indicated that the incidence in concurrent controls was at the lower limit of the historical control range. There was no evidence of progression to malignancy. Notably, carcinomas demonstrated a negative trend with decreasing tumor incidence with increasing dose. Pancreatic tumors were not observed in the other 7 rat studies, including 4 other studies performed in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981). Furthermore, pancreatic tumors were not observed in the 6 mouse bioassays.

Hepatocellular Tumors

Hepatocellular tumors were evaluated in 2 rat carcinogenicity studies (Stout and Ruecker, 1990; Brammer, 2001). In Table 4.4, the raw p-value for trend was statistically significant for adenomas in male Sprague-Dawley rats (Stout and Ruecker, 1990); however, it was not statistically significant following adjustment for multiple comparisons. There were no statistically significant pairwise comparisons. Historical control data from the performing laboratory indicated that the incidence of hepatocellular tumors was within the historical control range at all doses. Closer examination of the tumor incidence indicated that the data fluctuated with no tumors observed in concurrent controls or the mid-dose and increases seen at the low-dose and high-dose. In Table 4.10, a statistically significant trend was observed for adenomas in male Wistar rats (adjusted p-value = 0.029) (Brammer, 2001). For pairwise comparisons, the raw p-value was statistically significant at the highest dose tested (1214 mg/kg/day); however, it was not statistically significant following adjustment for multiple comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect in both studies. There was no evidence of progression to malignancy. In particular, carcinomas demonstrated a negative trend with decreasing tumor incidence with increasing dose. Hepatocellular tumors were not observed in the other 6 rat studies, including 4 other studies in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981) and 2 other studies in Wistar rats (Suresh, 1996; Wood *et al.* 2009a) the same rat strains. Furthermore, hepatocellular tumors were not observed in the 6 mouse bioassays.

Thyroid Tumors

In Table 4.6, there were no statistically significant trends or pairwise comparisons were observed for thyroid C-cell tumors in male Sprague-Dawley rats (Stout and Ruecker, 1990). In Table 4.7, a statistically significant trend for adenomas and combined adenomas/carcinomas was observed with raw p-values in female Sprague-Dawley rats (Stout and Ruecker, 1990); however, the trends were not statistically significant with adjustment for multiple comparisons. There were no statistically significant pairwise comparisons observed at any dose. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Thyroid tumors were not observed in the other 7 rat studies, including 4 other studies performed in Sprague-Dawley rats (Atkinson *et al.*, 1993a; Pavkov and Wyand, 1987; Enemoto, 1997; Lankas, 1981). Furthermore, thyroid tumors were not observed in the 6 mouse bioassays.

Mammary Gland Tumors
In Table 4.11, raw trend p-values were statistically significant for mammary gland adenocarcinomas and combined adenomas/adenocarcinomas in female Wistar rats (Wood *et al.*, 2009a); however, only the combined p-value for trend remained statistically significant following adjustment for multiple comparison (adjusted p-value = 0.028). There were no statistically significant pairwise comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Mammary gland tumors were not observed in the other 7 rat studies, including 2 other studies performed in Wistar rats (Brammer, 2001; Suresh, 1996). Furthermore, mammary gland tumors were not observed in the 6 mouse bioassays.

Kidney Tumors
In Table 4.13, there were no statistically significant trend observed for renal tubular cell tumors in male CD-1 mice (Knezevich and Hogan, 1983). This study tested up to almost 5000 mg/kg/day. Historical control data from the performing laboratory indicated that the incidence of adenomas was within the historical control range. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Kidney tumors were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Atkinson *et al.*, 1993b; Wood *et al.*, 2009b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, kidney tumors were not observed in the 8 rat bioassays.

Hemangiosarcomas
In Table 4.16, a statistically significant trend was observed for hemangiosarcomas in male CD-1 mice (adjusted p-value = 0.006) (Atkinson *et al.*, 1993b). There were no statistically significant pairwise comparisons. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. There was no evidence of progression to malignancy. Hemangiosarcomas are commonly observed in mice (generally more common in males for CD-1 strain) as both spontaneous and treatment-related tumors arising from endothelial cells. Hemangiosarcomas were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Wood *et al.*, 2009b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, hemangiosarcomas were not observed in the 8 rat bioassays.

Lung Tumors
In Table 4.17, the raw p-value for trend was observed for lung adenocarcinomas; however, the trend was not statistically significant following adjustment for multiple comparisons in male CD-1 mice (Wood *et al.*, 2009b). There were no statistically significant pairwise comparisons. Tumor incidences at all doses were within the historical control range for the performing laboratory. There was a lack of preneoplastic or related non-neoplastic lesions to support a treatment-related effect. Lung tumors were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, lung tumors were not observed in the 8 rat bioassays.

Malignant Lymphoma
In Table 4.18, statistically significant trend was observed in male CD-1 mice (adjusted p-value = 0.025) (Wood *et al.*, 2009b). For pairwise comparisons, the raw p-value for the highest dose tested was statistically significant; however, it was not statistically significant following adjustment for multiple comparisons. Malignant lymphoma was not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Sugimoto, 1997; Pavkov and Turnier, 1987). Furthermore, malignant lymphoma was not observed in the 8 rat bioassays.

Hemangiomas
In Table 4.19, a statistically significant trend was observed in female CD-1 mice (adjusted p-value = 0.005) (Sugimoto, 1997). For pairwise comparisons, the incidence at the highest dose tested was statistically significant (adjusted p-value = 0.035). The highest dose tested in this study was more than 4X the limit dose. Hemangiomas were not observed in the other 5 mouse studies, including 4 other studies performed in CD-1 mice (Knezevich and Hogan, 1983; Atkinson *et al.*, 1993b; Wood *et al.*, 2009b; Pavkov and Turnier, 1987). Furthermore, hemangiomas were not observed in the 8 rat bioassays.

Based on the weight-of-evidence evaluations, the agency has concluded that none of the tumors evaluated in individual rat and mouse carcinogenicity studies are treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Tumors seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses.

5.0 Data Evaluation of Genetic Toxicity

5.1 Introduction

Genotoxicity is a broad term for any damage to the genetic material, whether the damage is transient or permanent. Transient damage refers to unintended modifications to the structure of DNA, which may or may not undergo successful repair. Permanent damage refers to heritable changes in the DNA sequence, known as mutations. Types of mutations include: 1) changes in single base pairs, partial, single or multiple genes, or chromosomes, 2) breaks in chromosomes that result in transmissible deletion, duplication or rearrangement of chromosome segments, and 3) mitotic recombination (OECD, 2015). In somatic cells, DNA-reactive chemicals can cause cancer if the mutations occur within regulatory genes that control cell growth, cell division and differentiation, such as proto-oncogenes, tumor suppressor genes and/or DNA damage response genes (OECD, 2015). Additionally, DNA damage may signal the cell to undergo apoptosis (cell death) rather than cell division and, therefore, the damage is not "fixed" as a mutation and is not passed along to daughter cells.

Evaluation of genotoxicity data entails a weight-of-evidence approach that includes consideration of the various types of genetic damage that can occur. Since no single genotoxicity assay evaluates the many types of genetic alterations that can be induced by a chemical, one must employ a battery of genotoxicity tests to adequately cover all the genetic endpoints important for regulatory decisions. EPA, like other regulatory agencies, considers genotoxicity information as part of the weight of evidence when assessing the potential of a chemical to induce cancer in humans. Under FIFRA, OPP requires genotoxicity tests of the technical grade active ingredient for the registration of both food and non-food use pesticides. The current genotoxicity test battery (40 CFR Part 158.500) for pesticide registration consists of:

1) Bacterial reverse mutation test (typically conducted in bacteria strains *Salmonella typhimurium* and *Escherichia coli*),

2) *in vitro* mammalian (forward) gene mutation *and in vitro* mammalian chromosomal aberration test, and

3) *in vivo* test for micronucleus induction (mammalian erythrocyte micronucleus test) *or in vivo* chromosomal aberration test (mammalian bone marrow chromosomal aberration test).

In cases where equivocal or inconsistent results are obtained for the same endpoint in different test systems, additional testing may be required. Test Guidelines on how to conduct the genotoxicity tests have been published by the agency and have been harmonized with the Organization for Economic Cooperation and Development (OECD, 2015; Cimino 2006). These guidelines identify specific test species, genetic endpoints, test conditions, exposure durations as well information on how to report data and interpret the results. The test guidelines provide a level of consistency and predictability for regulatory compliance and regulatory decision making.

5.2 Scope of the Assessment Considerations for Study Quality Evaluation

Previous genotoxicity assessments conducted as part of the CARC reviews for glyphosate in 1991 and 2015, considered only studies conducted with glyphosate technical and included only studies that provided adequate characterization of the test material (*i.e*. purity information provided). In the current analysis, a fit-for-purpose systematic review process was conducted to identify relevant genotoxicity data from regulatory studies and published literature from open sources (published and unpublished) for both glyphosate technical and glyphosate-based formulations. Studies conducted with glyphosate formulations that were identified and considered relevant for genotoxicity evaluation are summarized in table form in Appendix F. As described in Section 7.0 of this document, glyphosate formulations are hypothesized to be more toxic than glyphosate alone. The agency is collaborating with NTP to systematically investigate the mechanism(s) of toxicity for glyphosate and glyphosate formulations. However, the focus of this section is the genotoxic potential of glyphosate technical.

As described previously in Section 2.1.3, the list of studies identified in this process were also cross-referenced with genotoxicity review articles for glyphosate from the open literature [Kier and Kirkland (2013), and Williams *et al.* (2000)], as well as recent international evaluations of glyphosate (IARC 2015, EFSA 2015, JMPR 2016). The current analysis also includes studies conducted by other registrants that were not previously available to the agency. Sixteen studies for glyphosate technical that were included in Kier and Kirkland (2013) were not available to the agency; therefore, data and study summaries provided in the review articles were relied upon in the current review and are identified in the data tables with a footnote. The Kier and Kirkland (2013) article serves as the original publication for these studies and provided relevant information on study design and conditions as well as summary data. The data set includes *in vitro* and *in vivo* studies conducted in mammalian systems, with the exception of standard bacterial test strains, which have a long history of detecting chemicals that are mutagenic in humans. Studies conducted in non-mammalian species (e.g. worms, fish, reptiles, plants), were excluded because they were considered to be not relevant for informing genotoxic risk in humans. Several epidemiological studies that evaluated biomarkers for genotoxicity were not included in this evaluation because these studies were assigned a low quality ranking as described in Section 3.3.

When evaluating the quality of the published and unpublished data for inclusion in the analysis, the agency considered the reporting quality (how well a study was reported), the study design and how well the study was conducted. Critical elements in study design and interpretation for genotoxicity tests are described in the various EPA and OECD test guidelines. Elements such as test conditions (e.g. solubility, pH, osmolarity, and cytotoxicity) and study design (e.g. number of test organisms, doses selected, use of positive and negative controls; blinded evaluation) were used to evaluate the quality of published and non-published studies. In cases where inappropriate testing conditions or study design clearly had an impact on the outcome the study, the study was excluded from the analysis. For example, early studies by Majeska (1982) were excluded from the analysis since it was clearly demonstrated that altered pH by the test chemical can result in false positive responses in several of *in vitro* genotoxicity tests (Majeska, 1985d,e,f). In other cases, particularly with the published literature studies, where test conditions and/or study design differed from what is generally considered as acceptable

following in the EPA or OECD guidelines, the differences are noted, but the studies were not excluded from analysis unless the condition made the study unreliable. Summaries of relevant genotoxicity studies can be found in TXR# 0057499. Studies that were excluded from the analysis are listed in Appendix G.

The studies evaluating the genetic toxicity of the active ingredient glyphosate are presented in the following sections according to the type of genetic endpoints evaluated: mutations, chromosomal aberrations and other assays evaluating DNA damage. *In vitro* and *in vivo* assays are discussed separately according to the genetic endpoint. For the purpose of this analysis, glyphosate and its salts are considered together when evaluating the genotoxic potential of the active ingredient glyphosate.

5.3 Tests for Gene Mutations for Glyphosate Technical

5.3.1 Bacterial Mutagenicity Assays

Bacteria have traditionally been employed as a primary test organism for the detection of chemical mutagens. The bacterial reverse mutation assay is routinely performed in the test strains of *Salmonella typhimurium* and *Escherichia coli.* These test strains are mutant strains that are deficient for the synthesis of an essential amino acid. The assay detects mutations that revert the test strains back to wild type for amino acid synthesis and the revertants are identified by their ability to grow in culture medium deficient of the specific amino acid(s). This mutagenicity test identifies point mutations, which includes base substitutions and deletions and insertions of up to a few base pairs (OECD 471). The tests are typically conducted in the presence and absence of an exogenous source of metabolic activation (e.g., S9 microsomal fraction of activated liver homogenates) to identify potential mutagenic metabolites.

Glyphosate has been extensively evaluated for its potential to induce mutations in bacteria. Most of the studies considered consist of the full battery of bacterial strains (*i.e.* the recommend strains in EPA and OECD Test Guidelines) and were evaluated at appropriate test concentrations (up to cytotoxic or assay limit concentrations).

EPA identified 27 studies that tested glyphosate technical in bacterial mutagenicity assays by means of the standard plate incorporation method or the pre-incubation modification of the standard assay. Glyphosate was negative in the presence and absence of metabolic activation in all the studies. The results of the bacterial reversion mutation assays evaluating glyphosate technical are presented in Table 5.1

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	**Test System**	**Concentrations**	**Purity**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA98 and TA100 and WP *uvrA* ± S9	156-5000 µg/plate	95.68%	Negative ± S9	Akanuma (1995) [MRID 50017102]	
Bacterial Reverse Mutation	*S. typhimurium* TA535, TA1537, TA98 and TA100 and *E. coli* WP2P and WP2P *uvrA* ± S9	100-5000 µg/plate in DMSO	95.6% glyphosate acid	Negative ± S9	Callander (1996) [MRID 44320617]	
Bacterial Reverse Mutation	*S. typhimurium* TA 1535, TA1537, TA98 and TA100 and *E. coli* WP2P and WP2P *uvrA* ± S9	100-5000 µg/plate in water	60% potassium glyphosate salt	Negative ± S9	Callander (1999)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100 and TA102, ± S9	25-2000 µg in aqueous solution	Not provided	Negative ± S9	Chruscielska *et al*. (2000)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 ± S9	10-1000 µg/plate	98.4%	Negative ± S9	Flowers and Kier (1978) [MRID 00078620]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-3160 µg/plate	98.8%	Negative ± S9	Flügge (2009a)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-3160 µg/plate	96.4% technical	Negative ± S9	Flügge (2010b)[1]	

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	**Test System**	**Concentrations**	**Purity**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA98 and TA100	310-5000 µg/plate (+S9); 160-2500 µg/plate (−S9)	98.6%	Negative ± S9	Jensen (1991a) [MRID 49961502]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 ± S9	1-1000 µg/plate	98.05%	Negative ± S9	Miyaji (2008)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ± S9	5000 µg/plate	Not reported	Negative ± S9	Moriya *et al.* (1983)	
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA97, TA98 and TA100 ± S9	33-10,000 µg/plate	99%	Negative ± S9	NTP (1992)	Hamster and rat S9
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535 and TA97a ± S9	1-5000 µg/plate	61.27 % Glyphosate isopropyl-amine salt	Negative ± S9	Ranzani (2000)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 ± S9	648-5000 µg/plate	98.01%	Negative ± S9	Ribeiro do Val (2007) [MRID 50000903]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. Coli* WP2 *uvrA* ± S9	31.6-5000 µg/plate	96.0% technical	Negative ± S9	Schreib (2010)[1]	

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	**Test System**	**Concentrations**	**Purity**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100 and *E. coli* WP2 *hcr* ± S9	10-5000 µg/plate	98.4%	Negative ± S9	Shirasu *et al*. (1978) [MRID 00078619]	Published in Li & Long, 1988
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	3-5000 µg/plate (plate-incorporation), 33-5000 µg/plate (pre-incubation test)	95.1%	Negative ± S9	Sokolowski (2007a) [MRID 49957406]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	3-5000 µg/plate (plate–incorporation) 33 – 5000 µg/plate (pre-incubation test)	97.7%	Negative ± S9	Sokolowski (2007b) [MRID 49957407]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	3-5000 µg/plate (plate–incorporation) 33-5000 µg/plate (pre-incubation test)	95.0%	Negative ± S9	Sokolowski (2007c) [MRID 49957408]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	3-5000 µg/plate	96.66% technical	Negative ± S9	Sokolowski (2009a)[1]	

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	**Test System**	**Concentrations**	**Purity**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* pKM 101 and WP2 pKM 101 ± S9	3-5000 µg/plate	96.3% glyphosate acid	Negative ± S9	Sokolowski (2009b) [MRID 49961801]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	3-5000 µg/plate	97.16 %	Negative ± S9	Sokolowski (2010) [MRID 50000902]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ± S9	1-1000 µg/plate	96.0%	Negative ± S9	Suresh (1993a)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP *uvrA* ± S9	0-5000 µg/plate	95.3%	Negative ± S9	Thompson (1996) [MRID 49957409]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 ± S9	31.6-5000 µg/plate	98.2%	Negative ± S9	Wallner (2010)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98 and TA100 ± S9	25 µg/plate	Not reported	Negative ± S9	Wilderman and Nazar (1982)	Rat S9 and plant cell-free homogenates were used for metabolic activation

Table 5.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Technical.						
Test/ Endpoint	**Test System**	**Concentrations**	**Purity**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 ± S9	0.12-10 mg/plate –S9 0.56-15 mg/plate +S9	90% glyphosate trimesium salt	Negative ± S9	Majeska *et al.* (1982a) [MRID 00126612]	
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA98 and TA100 ± S9	0.005-50 µL/mL	55.6% glyphosate trimesium salt	Negative ± S9	Majeska (1985a) [MRID 00155527]	

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

5.3.2 *In vitro* Tests for Gene Mutations in Mammalian Cells

In vitro gene mutation studies in mammalian cells are conducted in cell lines with reporter genes for forward mutations. The most common reporter genes are the endogenous thymidine kinase (TK) gene, endogenous hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene and the xanthine-guanine phosphoribosyl transferase transgene (XPRT). Mutations that occur within these reporter genes result in mutant cells that are resistant to the cytotoxic effect of the pyrimidine analogue trifluorothymidine (for TK) or the purine analogue 6-thioguanine (for HPRT and XPRT) (OPPTS 870.5330). Suitable cell lines for this assay include L5178Y mouse lymphoma cells, Chinese hamster ovary (CHO) cells, hamster AS52 and V79 lung fibroblasts and human TK6 lymphoblastoid cells. Similar to other *in vitro* assays, chemicals are tested both in the presence and absence of S9 metabolic activation.

A total of four studies were conducted for (forward) mutations in mammalian cells (Table 5.3). Three studies were conducted with a high purity concentration of glyphosate technical (≥95.6%) and the remaining study was performed with glyphosate trimesium salt. In four of the assays, mouse lymphoma L5178Y $TK^{+/-}$ cells were the target organism and one was conducted in CHO cells with the HPRT endpoint. Glyphosate technical and the glyphosate trimesium salt were negative in the mouse lymphoma cell assays (Jensen, 1991b; Clay, 1996; Majesak, 1985b) when tested up to the current guideline limit concentration and glyphosate was negative in CHO/HPRT cells when tested up to cytotoxic concentrations (Li, 1983a).

Table 5.2. *In vitro* Mammalian Gene Mutation Assays: Glyphosate Technical.

Test/Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y $TK^{+/-}$ cells ± S9	296-1000 µg/mL	95.6%	Negative	Clay (1996)[1]	Relative survival was 90% (-S9) and 57% (+S9) at top concentration
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y $TK^{+/-}$ cells ± S9	520–4200 µg/mL (+S9); 610–5000 µg/mL (-S9)	98.6%	Negative	Jensen (1991b) [MRID 49961504]	Reported no significant reduction in cloning efficiency at any concentration.
Gene Mutations in Mammalian Cells	Chinese hamster ovary (CHO) cells, HPRT locus ± S9	500–25000 µg/mL (+S9); 500-22500 µg/mL (-S9)	98.7%	Negative	Li (1983a); [MRID 00132681]	Tested S9 from 1-10% Cytotoxic at 22.5 mg/mL (-S9, and with 1,2 and 10% S9) and at 17.5 mg/ml (10% S9)
Gene Mutations in Mammalian Cells	Mouse lymphoma L5178Y $TK^{+/-}$ cells ± S9	1-5 µl/mL	55.6% *Glyphosate trimesium salt*	Negative	Majeska (1985b) [MRID 00155530]	Negative with pH adjusted

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

5.4 *In vitro* Tests for Chromosomal Abnormalities

Cytogenetic assays are tests that can detect chemicals that cause structural chromosomal damage (clastogenicity) or affect the segregation of chromosomes during cell division and alter chromosome number (aneuploidy). Generally, there are two types of *in vitro* cytogenetic assays that identify chemicals inducing chromosomal abnormalities: chromosomal aberration assays and micronucleus assays. Although chromosomal damage observed in these assays are not considered heritable mutations, chemicals that can induce these types of chromosomal damage can also induce transmissible mutations to daughter cells indicating their role in cancer (Yauk *et al.*, 2015; OECD 2015). In addition, assays such as (fluorescence *in situ* hybridization (FISH)) can provide additional mechanistic information on the formation of chromosomal abnormalities. It is important to note that factors such as cytotoxicity, solubility of the test substance, changes in pH or osmolality play a significant role in the outcome of the assay. Like other *in vitro* assays, compounds are generally tested in the presence or absence of S9 metabolic activation to determine if metabolism affects the genotoxic activity of the parent compound and to determine if potential genotoxic metabolites are formed.

5.4.1 *In vitro* Mammalian Chromosomal Aberration Test

Chromosomal aberration assays detect both structural chromosomal and numerical aberrations. Structural chromosomal aberrations are of two types: chromatid and chromosome and include breaks, deletions and rearrangements (OPPTS 870.5375, OECD 2015). Numerical chromosomal aberrations generally result from the loss of an entire chromosome mostly due to damage in the spindle fiber resulting in aneuploidy. The types of cells that are most commonly used in chromosomal aberration assays include established cell lines such as Chinese hamster lung (CHL) and CHO cells or primary cell cultures such as human or other mammalian peripheral blood lymphocytes. In this assay, cells are typically sampled at a time equivalent to the length of approximately 1.5 cell cycles from the start of treatment. Prior to harvesting, cells are treated with Colcemid® or colchicine to arrest cells at the first metaphase stage of the cell cycle following the beginning of exposure to the test article. Once harvested, the cells are stained and metaphase cells are evaluated microscopically for various types of chromosome aberrations. (OECD TG 473). Data should be presented in a way that indicates the percentage of affected cells in the population of cells scored (e.g., % cells with aberrations or # aberrant cells/100 cells). Gaps should not be included in the analysis; they are scored but gaps alone in the absence of any additional chromosomal aberrations (e.g., a fragment or a ring chromosome) are not sufficient to define a cell as aberrant.

Glyphosate technical was evaluated in eight chromosomal aberrations tests to determine its potential to induce clastogenic effects *in vitro*. The findings are presented in Table 5.3. Six of the eight studies were negative. The two positive studies were both from the same laboratory where, Lioi *et al*. reported an increase in chromosomal aberrations at glyphosate concentrations of 8.5µM and above in bovine lymphocytes (Lioi *et al.*, 1998b) and at all concentrations of glyphosate tested (7-170 µM) in human lymphocytes (Lioi *et al.*, 1998a) following a 72-hour exposure period. No chromosomal aberrations were observed as a result of exposure to glyphosate in one study using CHO cells (Majeska, 1985c) and in two studies with CHL cells

(Matsumoto, 1995; and Wright, 1996). Sivikova and Dianovsky (2006) reported no statistically significant increases in chromosomal aberrations in bovine lymphocytes treated with glyphosate (62% pure) at concentrations up 1120 µM following 24-hour exposure. (Sivikova and Dianovsky, 2006). In studies conducted with human lymphocytes treated with glyphosate (≥95%) for 24-96 hours at concentrations, no increase in chromosomal aberrations were seen at concentrations as high as 6000 µM (Fox, 1998; and Manas *et al*., 2009).

5.4.2 *In vitro* Mammalian Micronucleus Test

The *in vitro* micronucleus test can detect the induction of micronuclei in the cytoplasm of cells in the interphase stage of the cell cycle. Micronuclei form from acentric chromosome fragments (i.e., chromosome fragments lacking a centromere) or when whole chromosomes are unable to migrate to the cellular poles during anaphase prior to cell division. (OECD 487). Thus, the micronucleus assay can detect both structural and numerical chromosomal changes. It should be noted, however, that additional work is required to distinguish whether induced micronuclei have arisen from a clastogenic versus an aneugenic mechanism, *e.g*., staining micronuclei to detect the presence of kinetochore proteins. The assay is typically performed with cell lines or primary cell cultures of human or rodent origin. The assay can be conducted with the addition of cytochalasin B which inhibits cytokinesis resulting in the formation of binucleated cells. The presence of binucleated cells, indicates that cells have undergone one round of mitosis, a necessary prerequisite for micronucleus formation.

Six studies evaluated glyphosate technical for its potential to induce micronuclei *in vitro* (Table 5.4). Four of the six studies were positive and the remaining two studies were equivocal. In a study by Koller *et al*. (2012), TR146 cells (derived from a human neck metastasis of buccal epithelial origin) were treated for 20 minutes with up to 20 mg/L (~0.12 mM) glyphosate (95%), the authors reported a statistically significant increase in binucleated cells with micronuclei at 15 (~0.09 mM) and 20 (~0.12 mM) mg/L, and also indicated significant apoptosis and necrosis at 20 mg/L. The short exposure period in this study was unusually short (20 minutes) and was conducted in a tumor cell line that had not been well characterized in regards to its degree of chromosomal instability and DNA damage and repair capacity. In another study, Roustan *et al*. (2014) reported positive findings +S9 only in CHO cells treated with glyphosate (unknown purity) at 10- 100 µg/mL with little evidence of a dose response over that concentration range.

Two other studies evaluated glyphosate technical in human lymphocytes (Mladinic *et al*., 2009a, 2009b). These studies used an exposure protocol that is different from the OECD recommendations for the *in vitro* micronucleus assay. OECD recommends that whole blood or isolated lymphocytes are cultured in the presence of a mitogen (e.g. phytohemagglutinin; PHA) prior to exposure of a test chemical in order to detect micronuclei formed via an aneugenic mechanism. However, in these two studies, blood cells were exposed to glyphosate for 4 hours, washed, and then treated with PHA to stimulate cell division. Both studies reported a statistically significant increase in micronucleated cells at 580 µg/mL (~3.4 mM), but not at lower concentrations, following 4-hour exposures in the presence of S9. The frequency of micronucleated cells (+S9) ranged from 11.3 to 28.7 in one study (Mladinic *et al*., 2009a) and 33.3 to 65.2 in the other study (Mladinic *et al*., 2009b) over the 1000-fold concentration range. No statistically significant increases in micronucleated cells were seen in either study in the absence of S9 activation. When cells were evaluated with vital stains, cells treated with 580

μg/mL showed a significant ($p<0.05$) increase in the percentage of cells undergoing apoptosis and necrosis compared to the negative controls.

Piesova *et al.* (2004, 2005) conducted two *in vitro* micronucleus studies using glyphosate technical (62%) up to 560 μM in bovine lymphocytes. In the 2004 study, bovine lymphocytes from two donors were treated for 24 or 48 hours without S9 metabolic activation, and for 2 hours (with and without S9 activation) or 48 hours (-S9) in the 2005 study. Both studies yielded similar results following 48-hour exposure to glyphosate. In both cases, the authors reported a weak induction of micronuclei in one donor at 280 μM and at 560 μM in the second donor. The induction was approximately 2-fold ($p < 0.05$), but with no clear dose response. No effects on micronuclei induction were seen at the 2- or 24-hour time points; however, with these early time points it is unlikely that one cell division has occurred during or after treatment.

Table 5.3. *In vitro* Tests for Chromosome Aberrations in Mammalian Cells- Glyphosate Technical						
Test/Endpoint	**Test System**	**Concentrations/ Conditions**	**Test Material Purity**	**Results**	**Reference**	**Comments**
In vitro Chromosomal Aberration	Chinese hamster ovary (CHO) cells	4-10 µl/mL, ± S9	55.6% *Glyphosate trimesium salt*	Negative	Majeska (1985c) [MRID 00155530]	pH adjusted (7.4-7.6)
In vitro Chromosomal Aberration	Chinese Hamster lung (CHL) cells	±S9: 0, 250, 500, 1000 and 2000 µg/mL; 24 and 48 h treatment - S9; 6 h treatment ±S9 harvest 24 h	95.68%	Negative	Matsumoto (1995) [MRID 50017106]	Decline in pH noted at 500 and 1000 µg/mL.
In vitro Chromosomal Aberration	Chinese hamster lung (CHL) cells	-S9: 24 & 48-hr exposure: 0-1250 µg/mL; +S9: 0-1250 µg/mL	95.3%	Negative	Wright (1996) [MRID 49957410]	Excessive decrease in pH >1250 µg/mL
In vitro Chromosomal Aberration	Bovine lymphocytes	-S9 only: 0, 7, 85 and 170 µM; 72 h exposure	≥98%	Positive (all concs.)	Lioi *et al.* (1998b)	
In vitro Chromosomal Aberration	Bovine lymphocytes	±S9: 0, 28, 56, 140, 280, 560 and 1120 µM; 24 h exposure	62.0%	Negative	Sivikova and Dianovsky (2006)	Decreased MI and PI at ≥ 560 µM
In vitro Chromosomal Aberration	Human lymphocytes	±S9: 100-1250 µg/mL cultures analyzed; 68 & 92 h	95.6%	Negative	Fox (1998) [MRID 49961803]	Excessive decrease in pH >1250 µg/mL
In vitro Chromosomal Aberration	Human lymphocytes	-S9 only: 0, 5.0, 8.5, 17.0 and 51.1 µM; 72 h exposure	≥98%	Positive ≥ 8.5 µM	Lioi *et al.* (1998a)	No significant ↓ in MI observed.
In vitro Chromosomal Aberration	Human lymphocytes	-S9: 0, 200, 1200 and 6000 µM; 48 h exposure	96.0%	Negative	Manas *et al.* (2009)	No toxicity observed up to 6000 µM

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.
CA= chromosomal aberrations, MI= mitotic index, PI= proliferation index.

Table 5.4. *In vitro* Tests for Micronuclei Induction in Mammalian Cells- Glyphosate Technical						
Test/ Endpoint	**Test System**	**Concentrations/ Conditions**	**Test Material Purity**	**Results**	**Reference**	**Comments**
In vitro Cytokinesis Block Micronucleus Assay (with FISH analysis)	TR146 cells (human-derived buccal carcinoma cell line)	10, 15 and 20 mg/L; 20-minute exposure.	95%	Positive Statistically significant ($p<0.05$) increase in MN at 15 and 20 mg/L.	Koller *et al.* (2012)	Apoptosis and necrosis reported at 20 mg/L Also reported ↑ in NB and NPB
In vitro Cytokinesis Block Micronucleus Test	CHO-K1 cells	5 - 100 µg/mL, ±S9	Not stated	Negative –S9 Positive +S9 at 10-100 µg/mL	Roustan *et al.*, (2014)	No clear dose response
In vitro Cytokinesis Block Micronucleus Test	Bovine lymphocytes (2 donors)	0, 28, 56, 140, 280 and 560 µM 24 & 48 h exposure	62%	24 h: Negative 48 h: Equivocal ↑ MN at 280 µM only (donor A) ↑ MN at 560 µM only (donor B)	Piesova, 2004	No dose-response No significant decrease in CBPI observed.
In vitro Cytokinesis Block Micronucleus Test	Bovine lymphocytes (2 donors)	0, 28, 56, 140, 280 and 560 µM; 2 h (±S9) and 48 h (-S9) exposure	62%	2 h: Negative 48 h: Equivocal ↑ MN at 280 µM only (donor A) and at 560 µM only (donor B)	Piesova, 2005	No dose-response; No significant decrease in CBPI observed. Metabolic activation had no effect on MN formation after 2 h exposure.

Table 5.4. *In vitro* Tests for Micronuclei Induction in Mammalian Cells- Glyphosate Technical

Test/ Endpoint	Test System	Concentrations/ Conditions	Test Material Purity	Results	Reference	Comments
In vitro Cytokinesis Block Micronucleus Assay (with FISH analysis)	Human lymphocytes (treated with cytochalasin B)	4h treatment ±S9; 0.5, 2.91, 3.50, 92.8 and 580 µg/mL; harvested 72 h	98.0%	Negative –S9 Positive +S9, ↑ MN at 580 µg/mL, but not at 0.5-92.8 µg/mL Also observed ↑ in NB at 580 µg/mL (±S9); ↑ NPB at 580 µg/mL (+S9)	Mladinic *et al.* (2009a)	Cells were exposed to glyphosate and washed prior to treatment with PHA. Authors did not report being blind to treatment.
In vitro Cytokinesis Block Micronucleus Assay (with FISH analysis)	Human lymphocytes (treated with cytochalasin B)	4h treatment ±S9; 0.5, 2.91, 3.50, 92.8 and 580 µg/mL	98%	Negative –S9 Positive +S9 ↑ MN at 580 µg/mL, but not at 0.5 -92.8 µg/mL ↑ apoptosis and necrosis at 580 µg/mL (-S9); ↑ apoptosis at ≥ 2.91 µg/mL and necrosis at 580 µg/mL (+S9) ↑ in NB at 580 µg/mL (±S9) and NPB at 580 µg/mL (+S9)	Mladinic *et al.* (2009b)	Cells were exposed to glyphosate and washed prior to treatment with PHA. Authors did not report being blind to treatment. .

CBPI= cytokinesis block proliferation index, FISH= fluorescent in situ hybridization; MN= micronuclei; NB= nuclear buds; NPB= nucleoplasmic bridges.

5.5 *In Vivo* Genetic Toxicology Tests

5.5.1 *In Vivo* Assays for Chromosomal Abnormalities

5.5.1.1 Mammalian Bone Marrow Chromosomal Aberration Assays

The *in vivo* mammalian bone marrow chromosomal assay detects the ability of a chemical to cause structural chromosomal damage in cells in the bone marrow. The assay is typically conducted in rodents (mouse or rat) and detects both chromosome-type and chromatid-type aberrations. Chromatid-type aberrations are expressed when a single chromatid break occurs and/or a reunion between chromatids, and chromosome-type aberrations result from damage expressed in both sister chromatids (OPPTS 870.5385). In this test, animals are exposed (typically via oral route or intraperitoneal injection) and sacrificed at sequential intervals. Prior to sacrifice, animals are treated with a spindle inhibitor such as colchicine or Colcemid® to arrest cells at metaphase. Chromosome preparations from the bone marrow are stained and scored for chromosomal aberrations. (OPPTS 870.5385). Generally, the optimal time to detect chromosomal aberrations in the bone marrow is 24 hours after treatment.

Three *in vivo* mammalian bone marrow chromosomal assays were conducted with glyphosate technical for regulatory purposes and all were negative (Table 5.8). In the first study, Sprague Dawley rats were administered glyphosate (98%) at 0 or 1000 mg/kg and the bone marrow was sampled at 6, 12 or 24 hours after dosing. No significant increase in bone marrow chromosomal aberrations were observed (Li, 1983b). In the second study, Swiss albino mice were treated twice by oral gavage (24 hours apart) with 0 or 5000 mg/kg glyphosate technical (96.8%) resulting in no significant increase in bone marrow chromosomal aberrations (Suresh, 1994). In a third study conducted with glyphosate trimesium salt, no increase in chromosomal aberrations were seen in the bone marrow of rats treated by oral gavage with up to 188 mg/kg (Majeska, 1982c).

5.5.1.2 Rodent Dominant Lethal Test

Dominant lethal mutations cause embryonic or fetal death. The induction of a dominant lethal mutation after exposure to a chemical indicates that the test chemical has affected the germinal tissue (sperm at some point in development, from stem cell to spermatocyte). Dominant lethal effects are considered to result from chromosomal damage (structural or numerical), but may also reflect gene mutations or systemic toxicity (OPPTS 870.5450, OECD 2016). In this test, male rodents are treated with the test material and mated with (untreated) virgin females. The female animals are sacrificed at an appropriate time and the uteri are examined to determine the number of implants, and live and dead embryos. Two dominant lethal studies were identified. One study was conducted in the rat (Suresh, 1992) where male rats were dosed by oral gavage with glyphosate up to 5000 mg/kg. The other study (Rodney, 1980) was conducted in male mice treated with up to 2000 mg/kg glyphosate (98.7%) by oral gavage. No significant increase in dominant lethal mutations were observed in either study (Table 5.5).

5.5.1.3 *In Vivo* Mammalian Erythrocyte Micronucleus Assays

The mammalian micronucleus test is the most commonly conducted *in vivo* test to detect clastogenic or aneugenic chemicals. The test identifies chemicals that induce micronuclei in proerythrocytes (progenitor cells) by assessing micronucleus frequency in immature erythrocytes (polychromatic erythrocytes, PCEs) sampled from the bone marrow or from the peripheral blood (reticulocytes). This test is typically conducted in mice or rats. When bone marrow erythroblasts develop into erythrocytes, the main nucleus is extruded following the final cell division (erythrocytes are the only mammalian cell that does not contain a nucleus). Any micronuclei formed after the final cell division may remain in the cytoplasm following extrusion of the main nucleus. The visualization of micronuclei is facilitated by the lack of a nucleus in these cells (OPPTS 870.5395, OECD 474). Micronuclei can originate from acentric chromosomes, lagging chromosome fragments, or whole chromosomes; thus, micronuclei are biomarkers of both altered chromosome structure or chromosome number. The assay is based on an increase in the frequency of micronucleated erythrocytes in treated animals, in either peripheral blood samples or bone marrow samples (OPPTS 870.5395). Additional mechanistic information on the formation of chromosomal abnormalities can be obtained from the incorporation of centromeric and telomeric fluorescent probes (FISH) assay. According to EPA test guidelines, a single dose of the test substance may be used in this test if the dose is the maximum tolerated dose (MTD), a dose that produces some indication of bone marrow cytotoxicity (e.g., a reduction in the proportion of immature erythrocytes (PCEs) to total erythrocytes by >50%) or a maximum limit dose of 5000 mg/kg. The routes of administration for this test are typically oral or intraperitoneal injection and generally involve a single administration.

Glyphosate technical has been extensively evaluated for micronuclei induction in *in vivo* studies. Fourteen studies were conducted for regulatory purposes, four were identified from the open literature, and one study was conducted by the U.S. National Toxicology Program (NTP). This included nine studies with administration of glyphosate by the intraperitoneal (i.p.) route and 10 studies by the oral route. The findings are presented in Table 5.10. Of the nine i.p. studies, seven (Costa, 2008; Chruscielska *et al.*, 2000; Durward, 2006; Gava, 2000; Marques, 1999; Rank *et al.*, 1993 and Zaccaria, 1996) were negative. These studies tested doses as high as 2016 mg/kg (single and double administration) with sampling times at 24- and 48-hours post-dose. Two positive findings were reported when glyphosate technical was administered by i.p. Bolognesi *et al.* (1997) reported a significant increase in micronuclei in the bone marrow of male Swiss CD mice 24 hours after i.p. treatment with 300 mg/kg glyphosate technical (99.9%). The dose in this study was administered as ½ dose (150 mg/kg) injections 24 hours apart to 3 male mice. Manas *et al.* (2009) evaluated glyphosate technical (96%) in BALB/c male and female mice (5/sex/dose) administered 50, 100 or 200 mg/kg by two i.p. injections, 24 hours apart. The results showed a significant increase in micronucleated erythrocytes at 200 mg/kg, but not at 50 or 100 mg/kg. It should be noted that doses that resulted in the positive responses in these two studies were above the reported i.p. LD50 value (130 mg/kg) for glyphosate in mice (NTP 1992).

Glyphosate technical was also evaluated in nine micronucleus assays with administration by the oral route in mice and one in the rat. Eight of the nine oral studies in the mouse were negative for micronuclei induction. The single positive response was seen in female mice treated with

two 5000 mg/kg doses (limit dose), 24 hours apart with bone marrow sampling at 24-hours post-dose (Suresh, 1993b). No increase was observed at lower doses (50 and 500 mg/kg) in females or at any dose in males. The eight negative oral studies in mice included single dose administrations of 5000 mg/kg and bone marrow analysis at 24, 48, and/or 72 hours (Jensen, 1991c; Fox and Mackay, 1996) and one or two administrations of glyphosate technical with top doses between 30 and 2000 mg/kg (Honarvar, 2005; Honarvar, 2008; Jones, 1999; and Zoriki-Hosmi, 2007). It should be noted that evaluations at 48 and 72 hours post dose may be too late to detect chemically-induced micronucleated PCEs in the bone marrow as these cells may have already migrated into the peripheral blood. No significant increase in micronucleated erythrocytes were seen in male or female mice following 13-weeks of dietary (feed) administration of glyphosate technical at doses up to 3393 mg/kg/day (NTP, 1992). In the single study that evaluated micronuclei induction in rats, glyphosate technical did not induce significant induce micronuclei in CD1 rats treated by oral gavage at doses up to 2000 mg/kg (Flügge, 2009b). When glyphosate trimesium salt was evaluated, no increase in micronuclei induction was seen in mice treated orally up to 1100 and 800 mg/kg in males and females, respectively (Majeska, 1987).

Table 5.5. *In Vivo* Tests for Chromosomal Aberrations in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Chromosomal Aberration Test	Sprague Dawley rats (males and females)	Intraperitoneal injection; sampled at 6, 12 and 24 h after treatment	0, 1000 mg/kg (6/sex/dose/sampling time)	98%	Negative	Li (1983b) [MRID 00132683]	No toxicity observed. A separate study using ^{14}C-glyphosate showed that glyphosate reaches BM 0.5 h after dosing with ½ life elimination at 7.6 h. Peak BM value was 400 ppm, corresponding to 2000 ppm plasma value.
Bone Marrow Chromosomal Aberration Test	Sprague Dawley rats (males and females) Vehicle: distilled water	Oral gavage, sampling after 6, 12, 24, 48 h and 5 d	0, 21, 63 and 188 mg/kg	58.5% *Glyphosate trimesium salt*	Negative	Majeska (1982c) [MRID 00132176]	
Bone Marrow Chromosomal Aberration Test	Swiss Albino mice (males and females) Vehicle: peanut oil	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 5000 mg/kg (5/sex/dose)	96.8%	Negative	Suresh (1994) [MRID 49987408]	Significant ($p<0.05$) decrease in bw of females at high dose.
Rodent Dominant Lethal Test	CD-1 mice Each dosed male mated with 2 females/week for 8 weeks	Oral gavage	0, 200, 800, and 2000 mg/kg	98.7%	Negative	Rodwell (1980) [MRID 00046364]	
Rodent Dominant Lethal Test	Wistar rat Each dosed male mated with 1 female/week for 10 weeks	Oral gavage	0, 200, 100 and 5000 mg/kg	96.8%	Negative	Suresh (1992) [MRID 49987404]	

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss CD1 mice (males only)	Intraperitoneal injection; 2 injections of half the dosage of 300 mg/kg 24 h apart; sampling at 6 and 24 h	0, 300 mg/kg (3/dose)	99.9%	Positive Stat significant increase in MN at 24 h	Bolognesi *et al.* (1997)	Material and methods indicate 3 animals/dose; however, Table 1 of article indicates 4 animals were evaluated.
Bone Marrow Micronucleus Test	Balb C mice (males and females) Vehicle: Saline	Intraperitoneal Injection (two injections, 24 h apart); sampling after 24 h (last treatment)	0, 50, 100, and 200 mg/kg (5/sex/dose)	96%	Positive ↑MN at 200 mg/kg, but not at 50 or 100 mg/kg	Manas *et al.* (2009)	No significant signs of toxicity observed.
Bone Marrow Micronucleus Test	C3H mice (males only) Vehicle: water	Intraperitoneal Injection (single treatment); sampling after 24, 48 and 72 h	0, 300 mg/kg	Not reported	Negative	Chruscielska *et al.* (2000)	
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: corn oil	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 15.62, 31.25, and 62.5 mg/kg (5/sex/dose)	980 g/kg Glyphosate technical	Negative#	Costa (2008)[1]	OECD guideline 474 #Was not tested up to limit dose and did not demonstrate that compound was tested up to toxic dose. No mention of BM toxicity or clinical signs.

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Crl:CD-1TM(ICR) BR mice (males only[1]) Vehicle: PBS	Intraperitoneal Injection (single treatment); sampling after 24 and 48 h (high dose only)	0, 150, 300 and 600 mg/kg (7/dose)	95.7%	Negative	Durward (2006) [MRID 49957411]	Clinical signs reported at ≥ 150 mg/kg. Significant ↓ in %PCEs reported at 24 h in 600 mg/kg group. ↑in MN PCEs observed at 600 mg/kg (1.9± 0.7 vs. 1.0 ± 1.2 control; $p<0.05$), at 24 h, but not 48 h, within historical control range.
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 1008, 2016, and 3024 mg/kg 5/sex/dose	612.7 g/kg (glyphosate technical Nufarm)	Negative	Gava (2000)[1]	LD50 was 4032 mg/kg Mortality observed in 1 animal at high dose (only 4 m/f scored for MPCEs). No effect on PCE/NCE.
Bone Marrow Micronucleus Test	Swiss Albino mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 187.5, 375 and 562.5 mg/kg 5/sex/dose	954.9 g/kg (glyphosate technical Nufarm)	Negative	Marques (1999) [MRID 49957412]	LD50 was 750 mg/kg No significant signs of toxicity observed in main study
Bone Marrow Micronucleus Test	NMRI-Bom mice	Intraperitoneal Injection (single treatment); sampling after 24 h (all doses) and 48 h (150 and 200 mg/kg)	0, 150, and 200 mg/kg (5/sex/dose)	glyphosate isopropylamine (purity not specified)	Negative	Rank *et al.* (1993)	

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss albino mice (males and females)	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 68, 137, and 206 mg/kg (	360 g/L	Negative	Zaccaria (1996) [MRID 49961501]	Doses selected were reported as corresponding to 25, 50 and 75% LD_{50}
Bone Marrow Micronucleus Test	CD-1 mice (males and females) Vehicle: saline	Oral gavage (single treatment); sampling after 24 and 48 h	0, 5000 mg/kg 5/sex/dose	95.6%	Negative	Fox and Mackay (1996) [MRID 44320619]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: PEG 400	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg 5 sex/dose	97.73%	Negative	Honarvar (2005)[1]	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males only) Vehicle: 0.5% carboxymethyl-cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/dose)	99.1%	Negative	Honarvar (2008) [MRID 49961802]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: 0.5% carboxymethyl-cellulose	Oral gavage (single treatment); sampling after 24, 48 and 72h	0, 5000 mg/kg; 5/sex/dose	98.6%	Negative	Jensen (1991c) [MRID 49961503]	No significant signs of toxicity observed
Bone Marrow Micronucleus Test	CD-1 mice (males only[1]) Vehicle: water	Oral gavage single treatment); sampling after 24 and 48 h	0, 2000 mg/kg 5/dose	59.3% potassium glyphosate salt	Negative	Jones (1999)[1]	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	Swiss albino mice; (males and females) Vehicle: peanut oil	Oral gavage (2 treatments, 24 h apart); sampling	0, 50, 500, 5000 mg/kg 5/sex/dose	96.8% glyphosate acid	Positive in females at 5000	Suresh (1993b) [MRID 49987407]	No significant signs of toxicity observed

Table 5.6. In Vivo Tests for Micronuclei Induction in Mammals- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
		after 24 h (last treatment)			mg/kg only. Negative in males at all doses		
Bone Marrow Micronucleus Test	Swiss mice (males only) Vehicle: corn oil	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 8, 15 and 30 mg/kg (6/dose)	980.1 g/kg	Negative	Zoriki Hosomi (2007) [MRID 50000901]	OECD guideline 474 No significant signs of toxicity observed
Bone Marrow Micronucleus Test	CD-1 mice (males and females) Vehicle: distilled water	Oral gavage, Sampling 24, 48 and 72 h after treatment	Males: 0, 700, 900 and 1100 mg/kg Females: 0, 400, 600 and 800 mg/kg	55.3% *Glyphosate trimesium salt*	Negative	Majeska (1987) [MRID 40214004]	
Bone Marrow Micronucleus Test	B6CF3 Mice (males and females)	Oral (dietary). MN assay conducted following 13-week feed study.	0, 205/213, 410/421, 811/844, 1678/1690 and 3393/3393 mg/kg (m/f) (10/sex/dose)	99%	Negative	NTP (1992)	
Bone Marrow Micronucleus Test	CD Rats (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	98.8%	Negative	Flügge (2009b)[1]	OECD guideline 474 No significant signs of toxicity observed

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline followed, test material purity, control chemicals and summary data tables.

[2]Only males tested; report indicated that there was no difference between sexes seen in range finding study.

CA= chromosomal aberrations, MPCE= micronucleated polychromatic erythrocytes, NCE= normochromatic erythrocytes, PCE=polychromatic erythrocytes.

5.6 Additional Genotoxicity Assays Evaluating Primary DNA Damage

There are a number of genotoxicity assays that evaluate primary DNA damage, but do not measure the consequence of the genetic damage (*i.e.,* mutation or chromosomal damage). As discussed in the Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines (OECD 2015), the endpoints measured in primary DNA damage tests such as DNA adducts, comet assay, or unscheduled DNA synthesis may lead to cell death or may initiate DNA repair, rather than a mutation. These types of assays can, however, provide mechanistic information when interpreting positive findings in other genotoxicity tests or when determining whether a chemical is acting through a mutagenic mode of action. Additionally, indirect mechanisms of DNA damage such as oxidative DNA damage can be detected by these test systems. Oxidative damage results from oxidative stress, which occurs when there is a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant defense systems. Normal cellular metabolism is a source of endogenous reactive oxygen species that accounts for background levels of oxidative damage in normal cells. Some types of oxidative damage are repairable while others lead to serious consequences in the cell. (Cooke et al, 2003). The various assays evaluating primary DNA damage in glyphosate technical are presented in Table 5.7. Details of the findings are discussed below.

Glyphosate technical is not electrophilic and is not considered to be DNA-reactive. In a study to evaluate the potential for glyphosate to directly interact with DNA, Peluso *et al.* (1998) reported that glyphosate technical did not form DNA adducts in mice when tested up to 270 mg/kg via i.p. Bolognesi *et al.* (1997) reported an increase in the oxidative damage biomarker 8-hydroxydeoxyguanosine (8-OHdG) in the liver 24 h after i.p. injection of 300 mg/kg in mice. No increase in 8-OHdG was seen in the kidney with glyphosate technical. The dose in this study was high (300 mg/kg) for an i.p. injection and within the i.p. LD_{50} range (134- 545 mg/kg) that has been reported elsewhere (WHO, 1994).

The comet assay, also known as single cell gel electrophoresis (SCGE), is a sensitive and rapid method to detect DNA strand breaks in individual cells. In this assay, individual cells are embedded in agarose. The cells are then lysed (which digests the cellular and nuclear membranes) and the DNA is allowed to unwind under alkaline or neutral conditions. During electrophoresis, chromatin (which is in a supercoiled state) that has undergone steric relaxation due to DNA damage migrates away from the nucleoid (nucleus) toward the anode, yielding images that resemble a comet. The intensity of the comet tail relative to the comet head reflects the amount of DNA breakage (Tice *et al.*, 2000; Collins *et al.*, 2008). The comet assay can detect single and double strand breaks resulting from direct interactions with DNA, alkali labile sites, or transient DNA breaks resulting during DNA excision repair. These types of strand breaks may be, (a) repaired with no persistent effect, (b) be lethal to the cell or (c) be fixed as a mutation (OECD TG 489). DNA strand breaks in the comet assay can be measured by endpoints such as percent tail DNA (also referred to as % tail intensity), tail length, and tail moment. However, % tail DNA is the recommended metric for evaluating and interpreting results using this assay (OECD TG 489).

The five studies that evaluated glyphosate technical using the comet assay are summarized in Table 5.12. Two of the studies were conducted using tumor cell lines. Koller *et al.* (2012) reported positive comet effects (increased tail intensity) in a human buccal carcinoma cell line (TR146) following a 20-minute treatment with ≥ 20 mg/L (~0.118 mM) glyphosate. Although no evidence of cytotoxicity was reported in this study, the authors did report an increase in apoptosis and necrosis at the same concentrations (≥ 20 mg/L) when the same cell line was tested for *in vitro* micronuclei induction (discussed previously). In a study using Hep-2 cells (presumably a HeLa cell derivative), Manas *et al.* (2009) reported a statistically significant increase in mean tail length, and tail intensity at all concentrations (3.0-7.5 mM) tested. In a comet study conducted on human lymphocytes, Alvarez-Moya *et al.* (2014) reported significant increases in tail length only (but not % tail DNA) following treatment with glyphosate concentrations of 0.7-700 µM. Mladinic *et al.* (2009a) evaluated DNA damage in non-dividing human lymphocytes (±S9) following treatment from 0.5 to 580 µg/mL using the standard alkaline comet method and a modified comet method that detects DNA damage due to oxidative damage (human 8-hydroxyguanidine DNA-glycosylase, hOGG1 comet method). In this study, the authors reported statistically significant increases in tail intensity at 3.5 µg/mL and higher in the absence of S9, with significance only at 580 µg/mL (~3.4 mM) in the presence of S9 using the alkaline method. This concentration also resulted in increased apoptosis and necrosis as well as an increase in plasma total antioxidant capacity (TAC) and changes in plasma lipid peroxidation (thiobarbituric reactive substances, TBARs); however, only a dose-related increase in tail length (not % tail DNA) was observed at 580 µg/mL (+S9) using the hOGG1 method. When the Manas *et al.* (2013) evaluated blood and liver cells following a 14-day drinking water study in mice treated with 40 and 400 mg/kg/day glyphosate, significant increases in tail intensity, tail length and tail moment were reported were observed at both doses in both tissues (except for DNA tail intensity in liver at 40 mg/kg); however, there were no substantial effects on oxidative stress measurements suggesting that DNA damage reported may not be due to oxidative damage.

The Unscheduled DNA Synthesis (UDS) test with mammalian liver cells *in vitro* identifies substances that induce DNA repair after excision and removal of a segment of damaged DNA. The test is typically conducted in liver cells, which have relatively few cells in the S-phase of the cell cycle. The assay measures the incorporation of radiolabeled nucleotide [^{3}H]-thymidine into DNA during the repair process in non-S phase cells. (OPPTS 870.5555). Substances that produce either a statistically significant dose-related increase or statistically significant and reproducible increase in ^{3}H-TdR incorporation in at least one test point are considered to be positive in this test. A UDS study that evaluated glyphosate technical in rat primary hepatocytes was negative (Williams, 1978). Glyphosate technical was also negative in a DNA repair test conducted in bacteria (Rec-A test) (Shirasu, 1978).

In an alkaline elution assay, which detects single strand DNA breaks, Bolognesi *et al.* (1997) reported an increase in single strand breaks (i.e. increased DNA elution rate) in the liver and kidney 4 hours after a single i.p. injection of 300 mg/kg. The elution rate returned to control levels at 24 hours. Glyphosate technical was also negative in a DNA repair test conducted in *Bacillus subtilis* H17 (rec$^+$) and M45 (rec$^-$) bacterial Rec-A test (Shirasu, 1978).

Finally, the sister chromatid exchange (SCE) test is an assay that can measure the consequence of primary DNA damage. The mechanism(s) of action for chemical induction of SCE is unclear. The SCE assay detects the exchange of DNA between two sister chromatid arms within a single chromosome. The assay can be performed *in vitro* or *in vivo*. Following exposure, cells/animals are treated with bromodeoxyuridine (BrdU) to allow for the differentiation of the two sister chromatids (harlequin staining) and prior to harvest are treated with a spindle inhibitor to accumulate cells in metaphase. The chromosome preparations are then stained and analyzed for SCEs (OPPTS 870.5900, 870.5915). The SCE studies that evaluated glyphosate technical are also presented in Table 12. Positive SCE findings were reported in all four studies; two evaluating bovine lymphocytes (Lioi, 1988b, Sivikova and Dianovksy, 2006) and two studies evaluating human lymphocytes (Lioi, 1988a; Bolognesi *et al.*, 1997). In all four studies the induction did not demonstrate a clear dose response.

Additionally, although it is recognized that mechanisms other than genotoxicity may be involved in cell transformation, glyphosate trimesium salt was evaluated in the Balb/3T cell transformation assay (an *in vitro* tumor formation assay) and was negative up to 5.0 mg/ml (Majeska, 1982b).

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
DNA Adducts ^{32}P-postlabeling	Swiss CD1 mice (males and females) Liver and kidney evaluated	Intraperitoneal injection; 24 h exposure	0, 130 and 270 mg/kg	Not reported	Negative	Peluso *et al.* (1998)	
DNA oxidative damage: 8-OHdG formation	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	0, 300 mg/kg (3/dose)	99.9%	Kidney: negative Liver: positive (24 h)	Bolognesi *et al.* (1997)	
Single-cell gel electrophoresis (SCGE) assays- Comet assay	TR146 cells (human-derived buccal epithelial cell line).	NA (*in vitro*)	-S9: 10-2000 mg/L; 20-minute exposure.	95%	Positive Increased DNA migration at >20 mg/L	Koller *et al.* (2012)	Also measured multiple cellular integrity parameters to assess cytotoxicity. No clear evidence of cytotoxicity seen except for increase in enzyme activity (indicative of membrane damage) in LDHe (extracellular lactate dehydrogenase) assay at >80 mg/L. No mention of monitoring pH
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Hep-2 cells	NA (*in vitro*)	0, 3, 4.5, 6, 7.5, 9, 12 and 15 mM	96%	Positive Stat. significant increase in mean tail length, and tail intensity at all concs.	Manas *et al.* (2009)	The authors did not report a source for the Hep-2 cells. The agency presumes that this is a HeLa derived cervical carcinoma cell line.

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Human lymphocytes	NA (*in vitro*)	0, 0.7, 7, 70, 700 µM	96%	Positive at all doses (increase in tail length only)	Alvarez-Moya *et al*., (2014)	Issues were identified with this study resulting in a low quality ranking. These include: 1) blood was washed with PBS and then held at 4º C for an indeterminate amount of time before exposure to glyphosate. (2) Cells were treated for 20 hours at room temperature. (3) The same amount of damage was reported across 2 orders of magnitude concentration.
Single-cell gel electrophoresis (SCGE) assays- Comet assay	Human lymphocytes; ±S9 Alkaline and hOOG1 Comet assays performed	NA (*in vitro*)	0, 0.5, 2.91, 3.5, 92.8 and 580 µg/mL	98%	Positive ±S9	Mladinic *et al.* (2009a)	<u>The alkaline comet assay</u> -S9: ↑ in mean tail length at 580 µg/mL and ↑ in tail intensity at ≥ 3.5 µg/mL). +S9: ↑ DNA tail length at ≥3.5 µg/mL. Tail intensity ↑ only at 580 µg/mL <u>hOOG1 comet assay</u>: -S9 no effect on tail length, ↑tail intensity only at 3.50 µg/mL +S9: ↑ tail length at 580 µg/mL, no effect on tail intensity compared to controls at any conc.

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Single-cell gel electrophoresis (SCGE) assays- Comet assay with oxidative stress measures	Balb/C mice; evaluated blood and liver	Drinking water (14 days)	0, 40, and 400 mg/kg	96%	Positive Blood and liver at both doses	Manas *et al.* (2013)	Only minor effects seen on oxidative stress measurements (TBARs, SOD, CAT)
Sister Chromatid Exchange (SCE)	Bovine lymphocytes (3 donors)	NA (*in vitro*)	-S9: 0, 17, 85 and 170 µM; 72 h exposure	≥98%	Positive Significant (p>0.05) increase in SC/cell at all concentrati ons	Lioi (1998b)	1.8-, 2.1-, 1.6-fold increases, respectively
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (*in vitro*)	-S9: 0, 5, 8.5, 17 and 51 µM; 72 h exposure	≥98%	Positive Significant (p>0.05) increase in SCE/cell at ≥ 8.5 µM	Lioi (1998a)	1.9-, 2.8-, and 2.6-fold increase at 8.5, 17 and 51 µM, respectively
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (*in vitro*)	-S9: 0, 0.33, 1,3 and 6 mg/mL; 72 h exposure	99.9%	Positive	Bolognesi *et al.* (1997)	Very limited information was provided on the methods used in this paper. Authors report a dose –dependent increase in SCE frequency; however, no statistical analysis for dose response was reported. Data presented graphically with no error bars.
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (*in vitro*)	28, 56, 140, 280, 560 and 1120 µM; 24 h exposure ±S9	62%	Positive	Sivikova and Dianovsky (2006)	The increases in SCEs observed did not show a clear concentration related increase across a 40-fold increase in the concentrations tested

Table 5.7 Assays for Detecting Primary DNA Damage- Glyphosate Technical.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material Purity	Results	Reference	Comments
Alkaline elution assay- DNA single strand breaks	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 8 and 24 h after injection	0, 300 mg/kg (3/dose)	99.9%	Positive (Increased elution rate) at 4 hours in liver and kidney At 24 h, elution rate returned to control levels	Bolognesi *et al.* (1997)	Return to control values may indicate DNA repair or reflect rapid elimination of compound
DNA Repair Test (Rec-A test)	*B. subtilis* H17 (rec+) and M45 (rec-)	NA (*in vitro*)	20-2000 µg/disk	98.4%	Negative	Shirasu (1978) [MRID 00078619]	
Unscheduled DNA synthesis (DNA repair)	F-344 rat primary hepatocytes	NA (*in vitro*)	0, 0.0125, 0.0625, 0.125, 0.6.5, 1.25, 12.5, 125 µg/mL	98%	Negative	Li and Long (1988)	
Cell Transformation Assay	BALB/3T cells	NA (*in vitro*)	0.313-5.0 mg/mL	90% *Glyphosate trimesium salt*	Negative	Majeska (1982b) [MRID 00126616]	

h- hour; CAT= catalase, G6PD= glucose 6-phosphate dehydrogenase, NA= not applicable, hOOG1 = TBARs= thiobarbituric acid reactive substances, SOD= superoxide dismutase

5.7 Summary and Discussion

The genotoxic potential of glyphosate has been extensively investigated using a variety of test systems and genetic endpoints. This assessment focuses only on test systems that the agency considered relevant for assessing genotoxic risks in humans. The totality of the genetic toxicology information was evaluated using a weight of evidence approach to determine the genotoxic potential of glyphosate. This involves the integration of *in vitro* and *in vivo* results as well as an overall evaluation of the quality, consistency, reproducibility, magnitude of response, dose-response relationship and relevance of the findings. In the weight of evidence analysis, studies evaluating endpoints that measured gene mutations and chromosomal aberrations (i.e. permanent DNA damage) were given more weight than endpoints reflecting DNA events that may be transient or reversible such as primary DNA damage (*e.g.,* comet assays). *In vivo* studies in mammals were given the greatest weight and more weight was given to doses and routes of administration that were considered relevant for evaluating genotoxic risk based on human exposure to glyphosate. Also, since the molecular mechanisms underlying the observation of SCEs are unclear and thus, the consequences of increased frequencies of SCEs are unclear, the data from this test were given low weight in the overall analysis. A summary of the various lines of evidence of considered in the weight of evidence evaluation for the genotoxic potential of the active ingredient glyphosate is presented below.

Evidence of primary DNA damage

Glyphosate technical is not considered to be electrophilic and did not induce DNA adducts in the liver or kidney at an i.p. dose of 270 mg/kg. However, evidence of DNA strand breaks was reported in a number mammalian cell studies using the comet assay. Additionally, transient increases in alkali labile sites in the liver and kidney of mice and an induction of 8-OHdG in DNA were seen in the livers of mice following i.p. injections with 300 mg/kg glyphosate. These effects were seen at high doses for the i.p. route in mice (LD_{50} for mouse =130 mg/kg; NTP, 1992). However, due to technical limitations identified in a number of these studies (e.g. use of cancer cell lines that have not been well-characterized, atypical exposure protocols and no indication of blind to treatment), caution should be exercised in interpreting the results.

In vitro mutations

Glyphosate technical was negative in all 39 studies for mutagenicity in bacteria. In the four studies that tested for gene mutations in mammalian cells *in vitro,* no increase in mutations were observed.

In vitro chromosomal alterations

Mixed results were observed in studies evaluating *in vitro* chromosomal alterations with glyphosate treatment. Three SCE studies reported positive findings (Lioi, 1998a, b; Bolognesi *et al*., 1997) bovine and human lymphocytes. As stated previously, low weight is given to SCE results in the overall analysis given the uncertainty regarding the consequence of increases in the frequencies of SCEs. The SCE responses were weak and not concentration dependent. Eight of the 10 studies measuring *in vitro* chromosomal aberrations were negative. The two positive

findings were reported by Lioi *et al.*, one study was conducted with bovine lymphocytes and the other with human lymphocytes. The authors reported positive findings in these studies at concentrations much lower than four other studies that reported negative results using the same cell types. Additionally, in both studies, Lioi *et al.* used an atypical exposure protocol of 72 hours which is very long for analyzing one round of mitosis. Furthermore, in both studies, nearly the same level effect for aberration frequency and percent of cells with aberrations were observed for the same concentrations of glyphosate and the two other chemicals tested in those experiments.

Four of the six studies evaluating micronuclei induction *in vitro* were positive and two showed equivocal results. Three of the positive responses required S9 activation, two conducted with human lymphocytes and one conducted with CHO cells. The remaining positive micronucleus study was conducted using a TR146 cells which is a tumor cell line derived from human buccal mucosa. The authors state that this cell line had not been previously used for genotoxicity testing. It is difficult to interpret any genotoxicity findings conducted in a tumor cell line that has not been well-characterized regarding its DNA damage response and repair capacity, and its degree of chromosomal instability.

Glyphosate was negative in all three L5178Y mouse lymphoma cell studies which may detect chromosomal damage in addition to mutations.

Mammalian *in vivo* chromosomal alterations

All three *in vivo* mammalian studies evaluating chromosomal aberrations with glyphosate technical were negative. Two studies were conducted in rats (i.p. and oral) and one was conducted in mice (oral). In addition, glyphosate was also negative in a rodent dominant lethal test. Glyphosate was negative in 15 of the 19 bone marrow micronucleus studies evaluated. In two of the positive studies, glyphosate technical was administered by i.p. injection. In these studies, the authors reported positive findings at doses of 200-300 mg/kg. Based on the available ADME data for glyphosate, assuming 30% oral absorption, an oral dose of ~700-1000 mg/kg would be needed to achieve a dose of 200-300 mg/kg in the blood. Seven other i.p. studies in mice reported no increase in micronuclei induction at doses up to 3000 mg/kg. The remaining positive finding was reported in an oral gavage study in mice where an approximately 2-fold increase in micronuclei were reported in females only at a dose of 5000 mg/kg, which is considerably higher than the current guideline recommended limit dose of 2000 mg/kg. The effect was not seen in the 7 other oral gavage studies in mice when glyphosate was tested at similar doses. In addition, glyphosate was negative for micronuclei induction following a 13-week dietary study with a dose up to approximately 3000 mg/kg/day. A negative finding was also reported in the only study that evaluated *in vivo* micronuclei induction in the rat using doses up to 2000 mg/kg.

In a meta-analytic review of micronuclei frequency across mammalian and non-mammalian species (primarily fish, amphibians, reptiles and plants), Ghisi *et al.* (2016), not surprisingly, reported that different responses were observed when comparing mammalian results to phylogenetically distant non-mammalian species for micronuclei induction. Their analyses included most, but not all, of the mammalian studies that the agency evaluated and determined to

be negative for micronuclei induction. The authors reported a statistically significant increase in micronuclei by the i.p. route across the studies in the data set they considered; however, when glyphosate was administered by the oral route (which is the most physiologically relevant route for human exposure to glyphosate), no significant difference was observed.

Conclusion for Glyphosate

The overall weight of evidence indicates that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route. When administered by i.p. injection, the micronucleus studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route, the effects occurred above the reported i.p. LD50 for mice and were not observed in other i.p. injection studies at similar or higher doses. While there is limited evidence genotoxic for effects in some *in vitro* experiments, i*n vivo* effects were given more weight than *in vitro* effects particularly when the same genetic endpoint was measured, which is consistent with current OECD guidance. The only positive findings reported *in vivo* were seen at relatively high doses that are not relevant for human health risk assessment.

6.0 Data Integration & Weight-of-Evidence Analysis Across Multiple Lines of Evidence

6.1 Background

In 2010, OPP developed a draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" which provides the foundation for evaluating multiple lines of scientific evidence (U.S. EPA, 2010). In 2016, a final version of the framework was published. OPP's framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety MOA/human relevance framework, which highlights the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek et al, 2014).

One of the key components of the agency's framework is the use of modified Bradford Hill Criteria (Hill, 1965) like those described in the 2005 Guidelines for Carcinogen Risk Assessment. These criteria are used to evaluate the experimental support considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight-of-evidence analysis.

6.2 Dose-Response and Temporal Concordance

Given the lack of consistent positive findings particularly at doses < 1000 mg/kg/day across the lines of evidence, lack of mechanistic understanding, and lack of biological activity in mammalian systems to the parent compound glyphosate, there are few data to assess key events in the biological pathway and any associated temporal or dose concordance. Temporal concordance can be assessed using the experimental animal studies and epidemiological studies that evaluated exposure prior to outcomes. Similarly, dose concordance can be assessed using findings of apical outcomes in experimental animal studies, as well as epidemiological studies that utilize exposure metrics that are stratified by the number of exposure days.

A prospective cohort study is designed to collect exposure information prior to the development of cancer. As such, exposure is known to occur before the outcome. In De Roos *et al.* (2005), a prospective cohort study, no association was observed between glyphosate exposure and all cancer outcomes evaluated in the AHS cohort. Although the median follow-up time following recruitment into the cohort was approximately 7 years in De Roos *et al.* (2005), an updated analysis of the AHS cohort has been recently published (Andreotti *et al.*, 2017), which included an extended follow-up period of 17.5 years and also did not report an association between glyphosate exposure and all cancer outcomes evaluated.

Two case-control studies evaluating the risk of NHL (Eriksson *et al.*, 2008 and McDuffie *et al.*, 2001) observed increased effect estimates in the highest exposure categories analyzed. Eriksson *et al.* (2008) found a greater effect estimate for subjects with >10 days (based on the median days of exposure among controls) and >10 years of exposure (for latency analysis) when compared to subjects with ≤10 days and 1-10 years of exposure, respectively; however, this analysis did not appear to adjust for co-exposures to other pesticides. By dividing the total number of exposed cases and controls using these exposure metrics, wider confidence intervals were observed due to smaller sample sizes, which reduces the reliability of the results to demonstrate a true

association. This may indicate that a longer follow-up time is needed to detect the risk for NHL; however, given the latency analysis of NHL was limited to Eriksson *et al.* (2008) and lack of NHL latency understanding in general, further studies are needed to determine the true latency of NHL. McDuffie *et al.* (2001), stratifying based on the average number of days per year of exposure, observed similar effect estimates in the lower exposure category (>0 and ≤2 days/year) while a greater effect estimate was observed in the highest exposure category (>2 days/year). The results from these two case-control studies conflict with the results observed in the cohort study (De Roos *et al.*, 2005; Andreotti *et al.*, 2017), where no dose-response was seen across three exposure categories (stratified by tertiles); however, the case-control studies did not adjust for co-exposure to other pesticides. It is also difficult to make conclusions regarding dose-response with only two exposure categories used for the analyses by Eriksson *et al.* (2008) and McDuffie *et al.* (2001). It should also be noted that these analyses combine all NHL subtypes, which may have etiological differences (Morton *et al.*, 2014). Although some studies did provide effect estimates for subtypes, as stated in Section 3.5.2, these were not considered in the current evaluation due to the limited sample sizes. At this time, there are no data available to evaluate dose-response for NHL subtypes.

With respect to animal carcinogenicity studies, key events in a MOA/AOP are evaluated to confirm that they precede tumor appearance. This temporal concordance evaluation cannot be conducted for glyphosate since a MOA/AOP has not been established. It was noted that no preneoplastic or related non-neoplastic lesions were reported in any of the animal carcinogenicity studies to support any observed tumors. Furthermore, genotoxicity assays did not support a direct mutagenic MOA. While there is limited evidence of genotoxicity in some *in vitro* endpoints, multiple *in vivo* studies do not support a genotoxic risk at relevant human exposure levels.

6.3 Strength, Consistency, and Specificity

A large database is available for evaluating the carcinogenicity potential of glyphosate. Across animal carcinogenicity and genotoxicity studies, results were consistent. For epidemiological studies, only one or two studies were available for almost all cancers investigated. The largest number of studies was available investigating NHL; however, there were conflicting results across studies.

In epidemiological studies, there was no evidence of an association between glyphosate exposure and solid tumors, leukemia, and HL. This conclusion is consistent with those recently conducted by IARC, EFSA, and JMPR. Furthermore, the available studies do not link glyphosate exposure to multiple myeloma.

At this time, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be supported based on the available data due to conflicting results. Chance and/or bias cannot be excluded as an explanation for observed associations. The magnitude of adjusted risk estimates for ever/never use were relatively small ranging from 1.0 (no association) to 1.85 in adjusted analyses, with the widest confidence intervals observed for the highest effect estimates indicating less reliability in these estimates. All of the ever/never estimates were not statistically significant with several effect estimates approximately equal to the null. There were

various limitations identified in Section 3.6 for these studies that could impact calculated effect estimates and explain the weak responses observed. Meta-risk ratios using these studies were also of small magnitude ranging from 1.3-1.5. As discussed in Section 3.6, meta-analyses should be interpreted with caution and are susceptible to the same limitations identified for individual studies.

Although none of the effect estimates were below 1 using the ever/never exposure metric, risk estimates were all below 1 (0.6-0.9) when using cumulative lifetime and intensity-weighted cumulative exposure metrics in the prospective cohort study (De Roos *et al.*, 2005; Andreotti *et al.,* 2017). As discussed in Section 6.2, two case-control studies that investigated an exposure-response relationship conflicted with the extensive analyses conducted for the AHS cohort. This may be due to differences in confounding control, differences associated with study design, limitations from small sample sizes, and/or, as some may suggest, a potentially short follow-up time in the cohort. It should also be noted that publication bias may play a role in this evaluation given there is a tendency to only publish positive results and potential concerns regarding glyphosate have only been raised in recent years.

A total of 14 (8 rat and 6 mouse) animal carcinogenicity studies with glyphosate, glyphosate acid, or glyphosate salts were analyzed for the current evaluation. None of the tumors evaluated were considered to be treatment-related based on weight-of-evidence evaluations. Although statistically significant trends were observed following adjustment for multiple comparisons in a limited number of studies, statistically significant pairwise comparisons were only observed in 2 studies indicating tumor incidences were generally similar to concurrent controls. Additionally, none of the tumor results were reproduced in other studies, including those testing the same animal strain with similar or higher dosing. Furthermore, the tumors lacked a monotonic dose-response and/or corroborating preneoplastic or related non-neoplastic lesions.

Over 80 genotoxicity studies with the active ingredient glyphosate were analyzed for the current evaluation. The overall weight-of-evidence indicates that there is no convincing evidence that glyphosate is genotoxic *in vivo* via the oral route. When administered via i.p. injection the studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route, the effects were not observed in other i.p. injection studies at similar or higher doses. Technical glyphosate was negative in all gene mutation studies. There was limited evidence of positive findings in studies evaluating primary DNA damage; however, as discussed in Section 5.6, the endpoints measured in these assays are less specific in regards to detecting permanent DNA changes (mutations) and can be attributed to other factors, such as cytotoxicity or cell culture conditions. Although some positive findings were reported for chromosomal alterations *in vitro*, these findings were limited to a few studies and are not supported by the *in vivo* studies that are the most relevant for human risk assessment.

Overall, there is remarkable consistency in the database for glyphosate across multiple lines of evidence. For NHL, observed associations in epidemiological studies were non-statistically significant and were of relatively small magnitude. Chance and/or bias cannot be excluded as an explanation for the observed associations. For all other cancer types, there were no associations found; however, only one or two studies were available for evaluation of most cancer types. Across species, strain, and laboratory, none of the tumors evaluated were considered to be

treatment-related based on weight-of-evidence evaluations. Statistically significant tumor results seen in individual studies were not reproduced in other studies, including those conducted using the same strain at similar or higher doses. The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic *in vivo*.

6.4 Biological Plausibility and Coherence

The Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) include the following guidance regarding the criteria of biological plausibility and coherence:

> "*evaluation of the biological plausibility of the associations observed in epidemiologic studies reflects consideration of both exposure-related factors and toxicological evidence relevant to identification of potential modes of action (MOAs). Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the biological markers evaluated in toxicologic and epidemiologic studies*. [p.39]."

The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic *in vivo*. Immunodeficiency is another plausible MOA associated with tumorigenesis (i.e., altered immune surveillance). Glyphosate was negative in an immunotoxicity study in mice at doses up to 1448 mg/kg/day (MRID 48934207). Additionally, the toxicology database for glyphosate does not reveal any evidence of immunotoxicity. Overall, the available data regarding non-cancer endpoints also do not provide any support for a carcinogenic process for glyphosate, and have shown glyphosate has relatively low toxicity. Laboratory animals generally display non-specific effects (e.g., clinical signs, reduced body weight) following glyphosate exposure at relatively high-doses, and no preneoplastic or related non-neoplastic lesions were observed to corroborate any of the observed tumors in the carcinogenicity studies.

As discussed in Section 4.2, metabolism studies demonstrate low oral absorption and rapid excretion of glyphosate. The data are not sufficient to determine whether linear kinetics is occurring at high doses where tumors were observed. In the carcinogenicity test guideline (OCSPP 870.4200) and the 2005 Guidelines for Carcinogen Risk Assessment, inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A study evaluating the toxicokinetic profile of glyphosate using multiple doses is needed to further investigate the pharmacokinetic properties between low- and high-dose levels.

Although many of the studies included in this document focus on the potential for glyphosate to cause a cancer outcome, the agency is also aware of a limited number of studies in the open literature that have shown glyphosate and its metabolite, AMPA, can inhibit proliferation and promote apoptosis in cancer cells indicating the compounds have potential to be developed into therapeutic drugs for cancer treatment (Li *et al,* 2013; Parajuli *et al.,* 2015; Parajuli *et al.,* 2016). It is unknown if this is due to lack of additional studies that have investigated these compounds for cancer treatment or if this may be due to publication bias. The bias towards only publishing positive and/or novel results can hamper the ability to evaluate whether there are plausible biological mechanisms for observed outcomes and/or sufficient information to support a cause-and-effect interpretation of an association. Overall, this further supports the need for

mechanistic data to elucidate the true mammalian MOA/AOP for glyphosate. There is a distinct lack of mechanistic understanding for the toxicity of glyphosate in mammals and the plant MOA is not relevant for mammalian systems.

The agency does not consider any of the tumors observed in the animal carcinogenicity studies to be treatment-related; however, some believe that the increased tumor incidences in various studies at the highest doses tested are treatment-related. In almost all of these studies, the highest dose tested was approximately equal to or greater than the limit dose (1000 mg/kg/day). It is very unlikely for people to be exposed to such large doses of glyphosate via the oral route. Glyphosate is registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops, as well as desiccant applications to several commodities. The highest dietary exposure value for any population subgroup in an unrefined chronic dietary analysis would be 0.23 mg/kg/day for children (1-2 years old). Since glyphosate also has residential uses, including application to turf, there is also the potential for children at this age to be exposed via incidental oral exposures (e.g., hand to mouth, object to mouth and soil ingestion) from playing on treated lawns. The highest exposure for the incidental oral and dermal exposures would be 0.16 mg/kg/day (from hand-to-mouth behaviors for children) and 0.08 mg/kg/day, respectively. Combining exposures from the dietary and residential exposures for children would, therefore, result in an aggregate exposure of 0.47 mg/kg/day. These calculations use a number of assumptions that have been extensively peer-reviewed[27] and yet the potential oral exposure of glyphosate for the most highly exposed residential population subgroup is more than 2,000 times lower than the highest doses tested in the animal carcinogenicity studies (see Appendix E for more details regarding these calculations). The maximum potential exposure calculated for occupational handlers would be 7 mg/kg/day, which is still significantly lower than the highest doses tested in the animal carcinogenicity studies. As a result, even though increased tumor incidences were observed in some of the animal carcinogenicity studies, the possibility of being exposed to these excessive dietary doses over time is considered implausible based on the currently registered use pattern and not relevant to human health risk assessment.

6.5 Uncertainty

When evaluating a database, it is also important to assess the uncertainties associated with the available data. When uncertainty is high there is less confidence in the exposure and effect estimates and, therefore, informs the reliability of results. Understanding the sources of uncertainty within a database can help characterize observed results and aid in developing new research with reduced uncertainty.

In some instances, the agency did not have access to all of the data underlying the studies analyzed for the current evaluation. This includes all of the epidemiological studies, 17 genotoxicity studies, and 1 animal carcinogenicity study. For these studies, the agency had to rely upon information the study authors reported. Without the raw data, statistical analyses could not be replicated or recalculated. On the other hand, studies that include full reports with detailed methodology, analytically measured doses, and individual animal data may provide a

[27] Using the 2012 Standard Operating Procedures for Residential Exposure Assessment. Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

higher level of confidence. It also allows the agency to perform its own evaluation of the data using current practices and policies.

Several uncertainties have already been identified throughout this document. There are numerous metabolism studies available for glyphosate; however, the data are not sufficient to determine whether linear kinetics is occurring at high doses where tumors were observed in animal carcinogenicity studies. In the carcinogenicity test guideline (OCSPP 870.4200) and the 2005 Guidelines for Carcinogen Risk Assessment, inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A study evaluating the toxicokinetic profile of glyphosate using multiple doses is needed to further investigate the pharmacokinetic properties between low- and high-dose levels.

With respect to the epidemiological data, the database is limited for each investigated cancer with only one or two studies available. Although numerous studies were used in the evaluation of NHL, the results were constrained by the limitations of the individual studies, such as small sample size, missing data, and control selection issues. The quality of the exposure assessment is a major concern since the validity of the overall study results depend in large part on the ability of the study to correctly quantify and classify a subject's exposure. There was no direct information on pesticide exposure or absorbed dose because the exposures were self-reported. All of the studies conducted exposure assessments through questionnaires and interviews that are susceptible to recall bias, which can result in exposure misclassification. The cohort study (De Roos *et al.*, 2005), which was given a high ranking, did not find an association between glyphosate exposure and NHL; however, it has been noted that the median follow-up time for this study was ~7 years. Recently, an updated analysis was published (Andreotti *et al.*, 2017) with an extended follow-up period of 17.5 years that addresses concerns regarding follow-up time. This study reported no association between glyphosate exposure and all lymphohematopoietic cancers, NHL, or any of its subtypes across exposure metrics. No association was observed in unlagged or lagged analyses, after adjustment for pesticides linked to NHL in previous AHS analyses, and after exclusion of multiple myeloma from the NHL grouping. Furthermore, with the increased use of glyphosate following the introduction of glyphosate-tolerant crops in 1996, there is a need for more recent studies since a large number of studies were conducted prior to 1996. As described in Section 1.1, the use pattern changed following the introduction of transgenic crops, which may impact overall effect estimates.

Another consideration is that farmers and other applicators apply formulations, not the active ingredient alone. It is possible that different formulations were used across and/or within the different epidemiological studies. Formulations are end-use products that are sold as a mixture of registered pesticidal active ingredients, such as glyphosate, and additional substances that increase the effectiveness of a pesticidal product, which are often referred to as "inert ingredients." For example, inert ingredients may act as a solvent to allow a pesticide active ingredient to penetrate a plant's outer surface, may facilitate and accentuate the dispersion of the product, or may extend the pesticide product's shelf-life[28]. Inert ingredients and the proportion of these inert ingredients vary across formulations. It has been hypothesized that glyphosate formulations may be more toxic than glyphosate alone. Glyphosate has been studied in a multitude of studies and there are studies that have been conducted on numerous formulations

[28] https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance

that contain glyphosate; however, there are relatively few research projects that have attempted to systematically compare glyphosate and the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations. This is one aspect of the uncertainty in the database that the agency has been working to address by developing a strategic research plan in collaboration with NTP (see Section 7.0).

It is recognized that these uncertainties exist for the current database; however, the available data are adequate for evaluating the carcinogenic potential of glyphosate and determine the cancer classification using the 2005 Guidelines for Carcinogen Risk Assessment. As discussed in Section 6.3, there are a large number of studies available and the database is remarkably consistent across these studies.

6.6 Evaluation of Cancer Classification per the 2005 EPA Guidelines for Carcinogen Risk Assessment

6.6.1 Introduction

In the 2005 Guidelines for Carcinogen Risk Assessment, five classification descriptors are provided:

- Carcinogenic to Humans
- Likely to be Carcinogenic to Humans
- Suggestive Evidence of Carcinogenic Potential
- Inadequate Information to Assess Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans

Descriptors are assigned using all available data from the multiple lines of evidence. The following text has been excerpted/summarized from the guidelines regarding these descriptors:

> Choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence. The weight-of-evidence, including the selected descriptor, is presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available. The descriptors and narratives are intended to permit sufficient flexibility to accommodate new scientific understanding and new testing methods. The descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full weight-of-evidence narrative. Rather than focusing simply on the descriptor, the entire range of information included in the weight-of-evidence narrative should be considered.

The weight-of-evidence presented in Sections 6.2-6.5 and based on the available epidemiological, animal carcinogenicity, and genotoxicity data for glyphosate was considered for each classification descriptor. For each descriptor, the guidelines provide examples and/or conditions for when the descriptor may be appropriate and the weight-of-evidence for glyphosate is assessed to determine which descriptor is supported by the available data. As stated in the 2005 EPA Guidelines for Carcinogen Risk Assessment, "the entire range of information included

in the weight-of-evidence should be considered". Based on all of the available data, the weight-of-evidence clearly do not support the descriptors "carcinogenic to humans" and "likely to be carcinogenic to humans" at this time. According to the 2005 Cancer Guidelines, "carcinogenic to humans" is appropriate "when there is convincing epidemiologic evidence of a causal association between human exposure and cancer." Similarly, "likely to be carcinogenic to humans" descriptor is appropriate "when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor."

In epidemiological studies, there was no evidence of an association between glyphosate exposure and solid tumors, leukemia, or HL. Furthermore, the available studies do not link glyphosate exposure to multiple myeloma. A conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data due to conflicting results and various limitations identified in studies investigating NHL. In 6 of the 14 animal carcinogenicity studies, no tumors were identified for evaluation. In the remaining 8 studies, the agency has concluded that none of the tumors evaluated in individual rat and mouse carcinogenicity studies are treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Tumors seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses. The tumor incidence increases in these studies were seen at or exceeding 1,000 mg/kg/day, except the testicular tumors in a single rat study, and these high doses would also not be considered relevant for human health risk assessment. The mammalian MOA/AOP is unknown for glyphosate and precursor events are unknown; however, the genotoxicity data were highly reproducible and consistent with a clear demonstration that glyphosate does not have a mutagenic MOA.

The descriptor "inadequate information to assess carcinogenic potential" is used when available data are judged inadequate for applying one of the other descriptors. Given the extensive size of the glyphosate database, which includes a multitude of well-designed and well-conducted studies, this classification descriptor is not supported. The epidemiological data at this time are limited and study results appear to be inconsistent for some cancer types. However, it is important to note that epidemiological studies are not available for most pesticides. Similarly, for most pesticides, generally, only two animal bioassays are available. EPA routinely evaluates human cancer potential using the small, more typical datasets. As such, for glyphosate, given the significant amount of information across multiple lines of evidence, the agency believes the database is sufficient to designate a cancer classification descriptor for glyphosate and that "inadequate information to assess carcinogenic potential" is not appropriate.

The remaining two cancer classification descriptors (*"Suggestive Evidence of Carcinogenic Potential"* and *"Not Likely to Be Carcinogenic to Humans")* from the 2005 EPA Guidelines for Carcinogen Risk Assessment are described in detail below. Subsequently, these descriptors are discussed in the context of whether the available evidence do or do not support them.

"Suggestive Evidence of Carcinogenic Potential"

This descriptor is appropriate when a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. It covers a spectrum of

evidence associated with varying levels of concern for carcinogenicity. Depending on the extent of the database, additional studies may or may not provide further insights.

Some examples of when this descriptor may be appropriate include the following:

- If a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight-of-evidence for the descriptor of "likely to be carcinogenic to humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system;
- If there is evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence;
- If there is a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed (when there is a high background rate of a specific tumor in animals of a particular sex and strain, then there may be biological factors operating independently of the agent being assessed that could be responsible for the development of the tumors). In this case, the reasons for determining that the tumors are not due to the agent are explained; or
- If there is a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.

"Not Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each MOA in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic.

This descriptor would be appropriate if any of the following was observed:

- Animal evidence demonstrates lack of carcinogenic effects in both sexes in well-designed and well-conducted studies in at least two appropriate animal species in the absence of other animal or human data suggesting a potential for cancer effects, or
- Convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans, or
- Convincing evidence that carcinogenic effects are not likely by a particular exposure route, or
- Convincing evidence that carcinogenic effects are not likely below a defined dose range.

6.6.2 Discussion of Evidence to Support Cancer Classification Descriptors

As stated above, the available data and weight-of-evidence clearly do not support the descriptors "carcinogenic to humans", "likely to be carcinogenic to humans", or "inadequate information to assess carcinogenic potential". The following discusses the remaining cancer classification descriptors and how the evidence does or does not support the descriptors.

It could be argued that the "suggestive evidence of carcinogenic potential" descriptor would be appropriate. The evidence to support this includes:

- Non-statistically significant effect estimates greater than the null were reported for NHL across studies and meta-analyses based on ever/never use ranged from 1.3-1.5.
- There was limited evidence of a possible exposure-response relationship between glyphosate exposure and NHL in case-control studies.
- In several animal carcinogenicity studies, a statistically significant trend was observed. In two studies, tumor incidences at the highest doses tested were statistically significant as compared to concurrent controls.
- Positive responses were observed in a limited number of genotoxicity assays evaluating chromosomal and primary DNA damage.

However, according to the 2005 EPA Guidelines for Carcinogen Risk Assessment, in order for the above evidence to support the "suggestive evidence of carcinogenic potential" descriptor, "the study generally would not be contradicted by other studies of equal quality in the same population group or experimental system". Furthermore, the guidelines state that "rather than focusing simply on the descriptor, the entire range of information included in the weight-of-evidence narrative should be considered". For the epidemiological studies evaluating NHL, several studies reported effect estimates approximately equal to the null. The widest confidence intervals were observed for the highest effect estimates indicating these effect estimate are less reliable. All of the effect ever/never estimates were non-statistically significant. There were conflicting results in exposure-response assessments investigating glyphosate exposure and the risk of NHL. Although two-case control studies (McDuffie *et al.*, 2001; Eriksson *et al.*, 2008) reported elevated effect estimates when analyzing for exposure-response relationships across two exposure categories, extensive analyses in a study of equal or higher quality (De Roos *et al.*, 2005) for cumulative lifetime exposure and intensity-weighted cumulative exposure contradicted these results reporting effect estimates less than null (ranging from 0.6-0.9) when analyzing across tertiles and these analyses were further supported by the recent evaluation of the AHS cohort by Andreotti *et al.* (2017). Furthermore, the two-case control studies did not account for co-exposure to other pesticides, which would be expected to cause inflated effect estimates. Various limitations that could impact the calculated effect estimate were identified for these studies and discussed in Section 3.6. The effect estimates greater than the null were not strengthened by other lines of evidence, as described in Sections 6.2-6.5.

In 6 (4 rat and 2 mouse) of the 14 animal carcinogenicity studies conducted with glyphosate, no tumors were identified for evaluation. In the remaining 8 studies, although statistically significant trends following adjustment for multiple comparisons were observed in 6 of these studies for different individual tumor types, almost all of these lacked pairwise significance

following adjustment for multiple comparisons. Pairwise significance was only observed at the highest dose tested for testicular tumors (Lankas, 1981) and hemangiomas (Sugimoto, 1997). For testicular tumors, a closer examination of the incidence data across doses did not demonstrate a monotonic dose response and the tumor findings were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. For hemangiomas, the statistical significance was seen at a dose more than 4X the limit dose, which would not be considered relevant for human health risk assessment. Furthermore, the tumor findings were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. In all of the animal carcinogenicity studies, there was no evidence of corroborating pre-neoplastic or related non-neoplastic lesions to support a treatment-related effect, including the testicular tumors. In a limited number of cases, the agency also considered historical control data to inform the relevance of tumor findings and these data generally indicated that incidence rates in the concurrent controls were unusually low and/or observed tumor incidences were within historical control ranges.

Although positive responses were observed in a limited number of genotoxicity assays evaluating chromosomal and primary DNA damage, the overall weight-of-evidence indicates that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route. When administered via i.p. injection the studies were predominantly negative. In the two cases where an increase in micronuclei were reported via this route of administration, the results were contradicted by numerous other studies at similar or higher doses using the same assays and route of administration. Technical glyphosate was negative in all gene mutation studies. There was limited evidence of positive findings in studies evaluating primary DNA damage; however, the endpoints measured in these assays are less specific in regards to detecting permanent DNA changes (mutations) and can be attributed to other factors, such as cytotoxicity or cell culture conditions. Although some positive findings were reported for chromosomal alterations *in vitro*, these findings were limited to a few studies and are not supported by the *in vivo* studies that are the most relevant for human risk assessment.

In summary, considering the entire range of information for the weight-of-evidence, the evidence outlined above to potentially support the "suggestive evidence of carcinogenic potential" descriptor are contradicted by other studies of equal or higher quality and, therefore, the data do not support this cancer classification descriptor.

For the "not likely to be carcinogenic to humans" descriptor, one of the considerations is whether there is "convincing evidence that carcinogenic effects are not likely below a defined dose range". In the case of glyphosate, the agency did not consider any of the tumors observed in the animal carcinogenicity studies to be treatment-related; however, some believe that the increased tumor incidences in various studies at the highest doses tested are treatment-related. In all of these studies, the highest dose tested was approximately equal to or greater than the limit dose (1000 mg/kg/day), except for the testicular tumors observed in a single study that were not considered treatment-related and were not reproduced in studies of equal quality, including studies in the same animal species and strain at similar or higher doses. In genotoxicity studies, assays with oral administration were negative except for one instance where an extremely high dose (5,000 mg/kg/day) was administered.

The 2005 EPA Guidelines for Carcinogen Risk Assessment also state that "weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed". Increased tumor incidence was typically observed at doses of 1,000 mg/kg/day or greater; however, none of these were considered treatment-related by the agency based on the weight-of-evidence evaluations. Additionally, the only *in vivo* positive assays seen in the genotoxicity studies were administered via i.p. injection at doses of 200 mg/kg/day and 300 mg/kg/day or orally at 5,000 mg/kg/day. These high doses are not considered relevant to human health risk assessment based on the currently registered use pattern for glyphosate. Maximum potential glyphosate exposure in residential and occupational settings have been estimated at 0.47 mg/kg/day and 7 mg/kg/day, respectively, which are well-below the doses necessary to elicit the effects seen in these animal carcinogenicity and genotoxicity studies. Additionally, non-linear kinetics may also be occurring at the high doses. The carcinogenicity test guidelines (OCSPP 870.4200 and OCSPP 870.4300) and the 2005 Guidelines for Carcinogen Risk Assessment state that inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms) should be avoided. A well-conducted pharmacokinetic study evaluating the toxicokinetic profile of glyphosate is needed to further investigate the toxicokinetic properties between high and low dose levels to ensure that inappropriate toxicokinetics is avoided.

Overall, there is not strong support for the "suggestive evidence of carcinogenic potential" cancer classification descriptor based on the weight-of-evidence, which includes the fact that even small, non-statistically significant changes observed in animal carcinogenicity and epidemiological studies were contradicted by studies of equal or higher quality. The strongest support is for "not likely to be carcinogenic to humans".

6.7 Proposed Conclusions Regarding the Carcinogenic Potential of Glyphosate

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

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

An extensive database exists for evaluating the carcinogenic potential of glyphosate, including 63 epidemiological studies, 14 animal carcinogenicity studies, and nearly 90 genotoxicity studies for the active ingredient glyphosate. These studies were evaluated for quality and results were analyzed across studies within each line of evidence. The modified Bradford Hill criteria were then used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance and biological plausibility. The available data at this time do no support a carcinogenic process for glyphosate. Overall, animal carcinogenicity and genotoxicity studies were remarkably consistent and did not demonstrate a clear association between glyphosate exposure and outcomes of interest related to carcinogenic potential. In epidemiological studies, there was no evidence of an association between glyphosate exposure and numerous cancer outcomes; however, due to conflicting results and various limitations identified in studies investigating NHL, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. Increases in tumor incidence were not considered treatment-related in any of the animal carcinogenicity studies. In 6 of these studies, no tumors were identified for evaluation. In the remaining studies, the tumors were not considered treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Additionally, tumor findings seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses. Furthermore, data from epidemiological and animal carcinogenicity studies do not reliably demonstrate expected dose-response relationships. In genotoxicity studies, there was no convincing evidence that glyphosate is genotoxic *in vivo* via the oral route.

For cancer descriptors, the available data and weight-of-evidence clearly do not support the descriptors “carcinogenic to humans”, “likely to be carcinogenic to humans”, or “inadequate information to assess carcinogenic potential”. For the “suggestive evidence of carcinogenic potential” descriptor, considerations could be looked at in isolation; however, following a thorough integrative weight-of-evidence evaluation of the available data, the database would not support this cancer descriptor. The strongest support is for “not likely to be carcinogenic to humans”.

This analysis integrating multiple lines of evidence highlights the need for mechanistic studies to elucidate the MOA/AOP of glyphosate, as well as additional epidemiology studies and updates from the AHS cohort study to further investigate the carcinogenic potential of glyphosate in humans. This evaluation focused on studies on the active ingredient glyphosate; however, additional research could also be performed to determine whether formulation components, such as surfactants, influence the toxicity of glyphosate formulations. The agency has been working on plans to initiate research given these identified data gaps and these plans are described in Section 7.0.

7.0 Collaborative Research Plan for Glyphosate and Glyphosate Formulations

As previously mentioned, some have believed that glyphosate formulations may be more toxic than glyphosate alone. 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 and the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across formulations.

The agency has been collaborating with the NTP Division 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. Four objectives were identified that laid out how research by NTP might contribute to these research questions: 1) compare the toxicity of glyphosate vs. formulations, as well as compare formulations vs. formulations, 2) provide publicly available toxicology data on cancer-related endpoints, 3) provide publicly available toxicology data on non-cancer endpoints, and 4) investigate the mechanisms of how glyphosate and formulations cause toxic effects.

As part of the first objective, NTP will investigate the differential biological activity of glyphosate, glyphosate formulations, and the individual components of formulations. The NTP Laboratory Branch generated preliminary data by exposing human hepatoma cells (HepG2) to five different glyphosate products bought off the shelf. The endpoint in the assay was cell viability, measured by ATP levels. The data, presented in Figure 7.1, demonstrate at-a-glance that formulations are not equally toxic and that the toxicity is not being driven by the amount of glyphosate in the formulations, at least for the endpoint of cell viability. This observation highlights how informative the data generated from this research can be to the overall research questions.

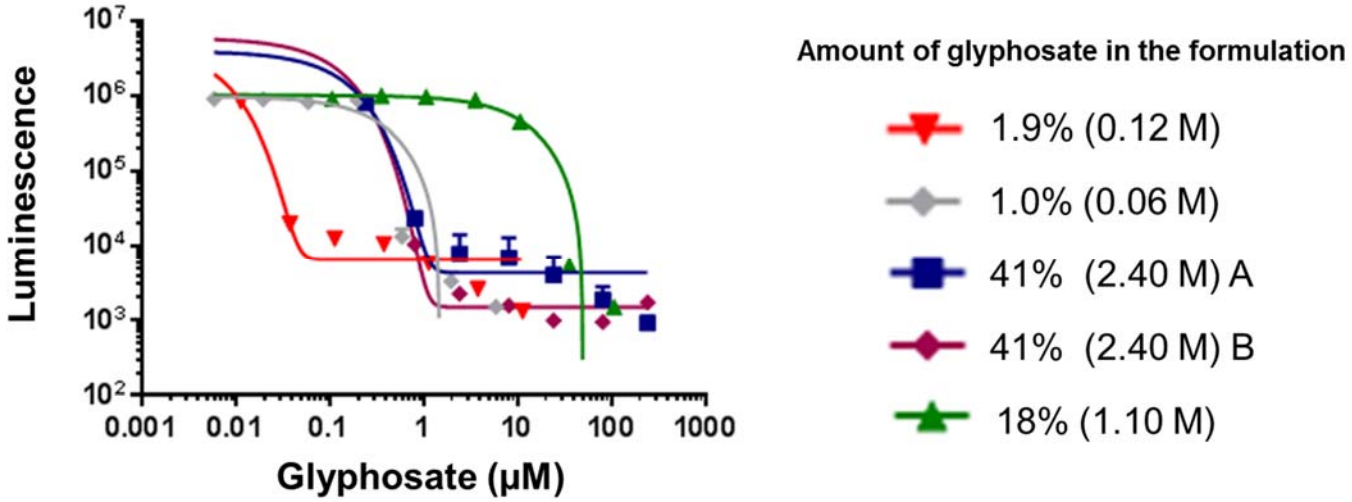

Figure 7.1. Results of HepG2 exposures following 24 hour incubation using different glyphosate formulations. Note: some of the formulations included other active ingredients besides glyphosate.

For the second objective, NTP will contribute to the publicly available knowledge-base describing the biological effects of glyphosate and formulations by conducting guideline studies addressing genotoxicity and studies that evaluate the oxidative stress potential. In order to organize publicly available data on glyphosate and formulations, IARC used 10 key characteristics of carcinogens as a way to help inform their conclusion (Smith *et al.*, 2016). Their review concluded that data were only available for two of these characteristics (genotoxicity and oxidative stress) and little to no information on the remaining characteristics was available. However, when members of a NTP workgroup looked at the available data included in the IARC review, the group did not agree with IARC that the data provided strong or clear evidence for either genotoxicity or induction of oxidative stress given protocol deficiencies that could produce questionable results.

Currently, the publicly available information regarding non-cancer endpoints for glyphosate and glyphosate formulations is limited. To begin to address the third objective, NTP will conduct a screening level analysis of the literature using text mining software, for studies regarding non-cancer endpoints resulting from glyphosate exposure. The resulting scoping report will describe the evidence base for health outcomes investigated in connection to glyphosate, as well as help identify data gaps.

As discussed in Section 6.0, there is a need for mechanistic studies to elucidate the MOA/AOP of glyphosate. Although there are data suggesting glyphosate may be genotoxic or cause oxidative stress, there is little mechanistic information to support these observations. For the last objective, NTP will use *in vitro* screening assays to gain mechanistic information on the effects of glyphosate and different formulations for a variety of endpoints and allow for direct comparisons among them. The screening approach will also allow for the identification of test substances that would be good candidates for further *in vivo* testing. Since *in vivo* findings in genetic toxicology testing are generally considered as having a greater relevance to humans than *in vitro* findings, it is valuable to confirm the results seen at the cellular level at the whole animal level.

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Appendix A. Journal articles obtained from open literature search

Abstract Only	Cebollero, L. R., et al. (2011). "Glyphosate based herbicides toxicity, a new approach." Toxicology Letters 205, Supplement: S233.
Abstract Only	Monroy, C. M., et al. (2004). "In vitro evaluation of glyphosate-induced DNA damage in fibrosarcoma cells HT1080 and Chinese hamster ovary (CHO) cells." Environ Mol Mutagen 44(3): 216-216.
Abstract Only	Ramos-Morales, P., et al. (2008). "Combined use of multiple biomarkers to evaluate the genotoxic activity of the herbicide Glyphosate." Environ Mol Mutagen 49(7): 577-577.
Abstract Only/Full article already identified	Sorahan, T. (2015). "Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data." Int J Environ Res Public Health 12(2): 1548-1559.
Article not in English	Kwiatkowska, M., et al. (2013). "GLYPHOSATE AND ITS FORMULATIONS - TOXICITY, OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE." Med Pr 64(5): 717-729.
Article not in English	Lawson, R. and E. Estrade-Chapellaz (1999). "Intoxication volontaire par le glufosinate (Basta®)." Annales Françaises d'Anesthésie et de Réanimation 18(9): 1025-1026.
Article not in English	Mañas, F., et al. (2009). "Aberraciones cromosómicas en trabajadores rurales de la Provincia de Córdoba expuestos a plaguicidas." BAG. Journal of basic and applied genetics 20(1): 0-0.
Article not in English	Martinez, A., et al. (2007). "[Cytotoxicity of the herbicide glyphosate in human peripheral blood mononuclear cells]." Biomedica 27(4): 594-604.
Article not in English	Monroy, C. M., et al. (2005). "[Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate]." Biomedica 25(3): 335-345.
Article not in English	Pieniazek, D., et al. (2003). "[Glyphosate--a non-toxic pesticide?]." Med Pr 54(6): 579-583.
Article not in English	Saratovskikh, E. A., et al. (2007). "Genotoxicity of the pestiside in Ames test and the possibility to formate the complexeses with DNA." Ekologicheskaya genetika V(3): 46-54.
Article not in English	В статье представлены результаты генотоксико логических, аллергологических и иммунологических исследований, проведенных в рамках медико-биологической оценки безопасности генно-инженерно-моди-фицированной кукурузы линии MON 88017, устойчивой к глифосату и жуку Diabrotica spp. Анализ данных, полученных при изучении уровня повреждений ДНК и уровня хромосомных аберраций, тяжести активного анафилактического шока и интенсивности гуморального иммунного ответа, состояния гуморального и клеточного звеньев иммунитета, не выявил какого-либо генотоксического, аллергенного, иммуномодулирующего и сенсибилизирующего действия ГМ-кукурузы линии MON 88017 по сравнению с ее традиционным аналогом.
Cancer treatment	Parajuli, K. R., et al. (2015). "Aminomethylphosphonic acid and methoxyacetic acid induce apoptosis in prostate cancer cells." Int J Mol Sci 16(5): 11750-11765.
Cancer treatment	Li, Q., et al. (2013). "Glyphosate and AMPA inhibit cancer cell growth through inhibiting intracellular glycine synthesis." Drug Des Devel Ther 7: 635-643.
Cancer treatment	Parajuli, K. R., et al. (2016). "Aminomethylphosphonic acid inhibits growth and metastasis of human prostate cancer in an orthotopic xenograft mouse model." Oncotarget 7(9): 10616-10626.
Correspondence article	Belle, R., et al. (2012). "LETTER TO THE EDITOR: TOXICITY OF ROUNDUP AND GLYPHOSATE." Journal of Toxicology and Environmental Health-Part B-Critical Reviews 15(4): 233-235.
Correspondence article	Carrasco, A. E. (2011). "Reply to the Letter to the Editor Regarding Our Article (Paganelli et al., 2010)." Chem Res Toxicol 24(5): 610-613.
Correspondence article	de Souza, L. and L. Macedo Oda (2013). "Letter to the editor." Food and Chemical Toxicology 53: 440.
Correspondence article	de Vendomois, J. S., et al. (2010). "Debate on GMOs Health Risks after Statistical Findings in Regulatory Tests." Int J Biol Sci 6(6): 590-598.
Correspondence article	Farmer, D. R., et al. (2005). "Glyphosate results revisited." Environ Health Perspect 113(6): A365-A366.
Correspondence article	Grunewald, W. and J. Bury (2013). "Comment on "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" by Seralini et al." Food and Chemical Toxicology 53: 447-448.
Correspondence article	Huang, K. and W. Xu (2013). "Reply to letter to the editor." Food and Chemical Toxicology 59: 811-812.
Correspondence article	Korsaeth, A., et al. (2015). "Comments on the recently published study: "Compositional differences in soybeans on the market: Glyphosate accumulates in Roundup Ready GM soybeans", by T. Bøhn, M.

	Cuhra, T. Traavik, M. Sanden, J. Fagan and R. Primicerio (Food Chemistry 2014, 153: 207–215)." Food Chemistry 172: 921-923.
Correspondence article	Ollivier, L. (2013). "A Comment on "Séralini, G.-E., et al., Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food Chem. Toxicol. (2012)," http://dx.doi.org/10.1016/j.fct.2012.08.005." Food and Chemical Toxicology 53: 458.
Correspondence article	Portier, C. J., et al. (2016). "Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)." J Epidemiol Community Health.
Correspondence article	Roberfroid, M. (2014). "Letter to the editor." Food and Chemical Toxicology 66: 385.
Correspondence article	Sanders, D., et al. (2013). "Comment on "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" by Seralini et al." Food and Chemical Toxicology 53: 450-453.
Correspondence article	Schorsch, F. (2013). "Serious inadequacies regarding the pathology data presented in the paper by Séralini et al. (2012)." Food and Chemical Toxicology 53: 465-466.
Correspondence article	Wallace Hayes, A. (2014). "Editor in Chief of Food and Chemical Toxicology answers questions on retraction." Food and Chemical Toxicology 65: 394-395.
Effects on cellular processes	Benachour, N. and G.-E. Seralini (2009). "Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells." Chem Res Toxicol 22(1): 97-105.
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Appendix B

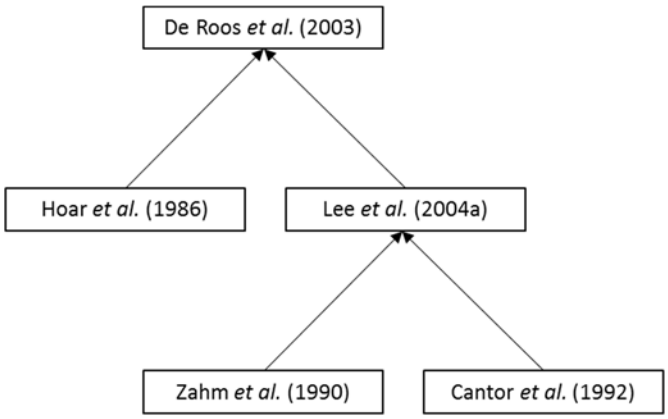

Figure B.1. Visual representation of studies included in De Roos *et al.* (2003).

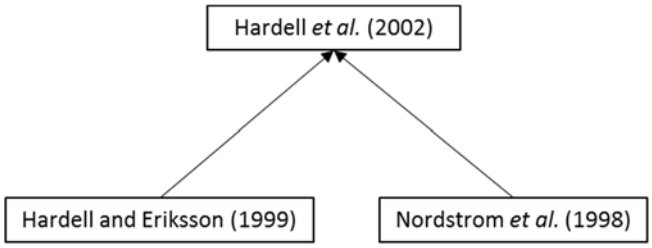

Figure B.2. Visual representation of studies included in Hardell *et al.* (2002).

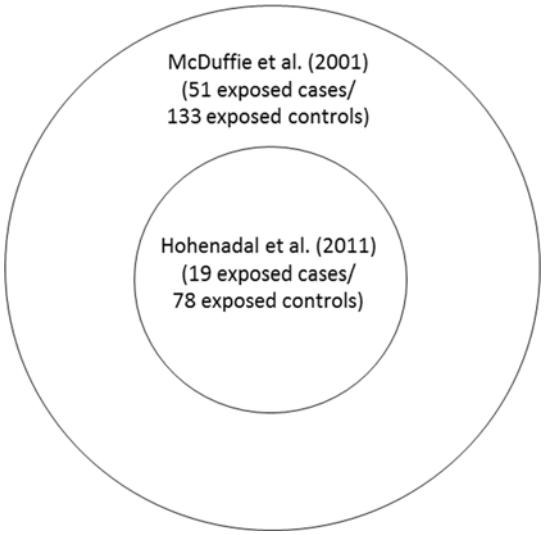

Figure B.3. Visual representation of the association between McDuffie *et al.* (2001) and the follow-up analysis by Hohenadal *et al.* (2011).

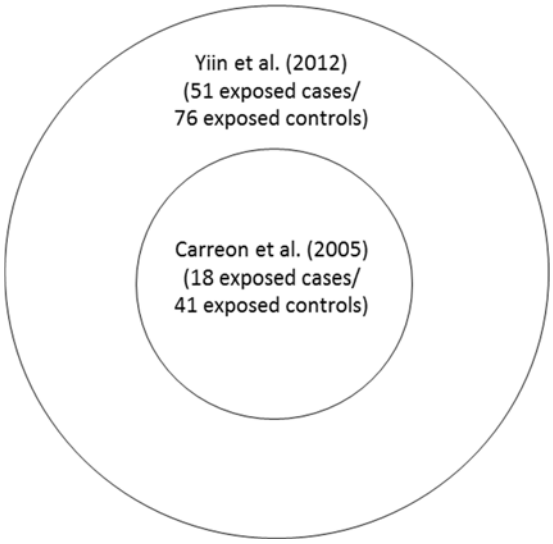

Figure B.4. Visual representation of the association between Carreon *et al.* (2005), which investigated gliomas in women only, and Yiin *et al.* (2012), which investigated both sexes.

Appendix C

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.

Study	Location	Study Years	Case Population	Control Population	Total Number of Subjects	Number of Glyphosate Exposed Cases	Proxy Use
Alavanja *et al.* (2003)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2001	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	566 cases 54,766 controls	not reported	No
Andreotti *et al.* (2009)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2004	Participants enrolled in AHS; licensed private and commercial applicators and spouses	Participants enrolled in AHS; licensed private and commercial applicators and spouses	93 cases (64 applicators, 29 spouses) 82,503 controls (52,721 applicators, 29,782 spouses)	55 cases 48,461 controls	No
Band *et al.* (2011)	Canada: British Columbia	1983-1990	Male residents in British Columbia identified as cancer patients in British Columbia Cancer Registry (excluding farmers that worked all outside British Columbia)	Male residents in British Columbia identified as cancer patients in British Columbia Cancer Registry (excluding farmers that worked all outside British Columbia) with other cancer sites excluding lung cancer and cancers of unknown primary site	1,153 cases 3,999 controls	25 cases 60 controls	Yes (included in adjustment)
Brown *et al.* (1990)	USA: Iowa and Minnesota	Iowa: 1981-1983; Minnesota: 1980-1982 Initial interview 1981-1984 and supplemental interviews (Iowa only) in 1987	White males (30 years or older) residing in Iowa or Minnesota diagnosed with leukemia	White males without lymphatic or hematopoietic cancer selected by random digit dialing (< age 65), Medicare records (age > 65) and state death certificate files (deceased controls) - frequency matched for 5-year age group, vital status, and state of residence	Initial: 578 cases; 1245 controls Supplemental: 92 cases; 211 controls	15 cases 49 controls	Yes (not evaluated)
Brown *et al.* (1993)	USA: Iowa	Iowa: 1981-1983; Interview 1981-1984	White males (30 years or older) residing in Iowa diagnosed with multiple myeloma	White males without lymphatic or hematopoietic cancer selected by random digit dialing (< age 65), Medicare records (age >	173 cases 650 controls	11 cases 40 controls	Yes (not evaluated)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
				65) and state death certificate files (deceased controls) - frequency matched for 5-year age group, vital status, and state of residence			
Cocco *et al.* (2013)	Czech Republic, France, Germany, Italy, Ireland, and Spain	1998-2004	Adult patients first diagnosed with lymphoma residing in the referral area of the participating centers	Controls from Germany and Italy were randomly selected by sampling from the general population, matched to cases on sex, 5-year age-group, and residence area. The rest of the centers used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases, and immunodeficient diseases	2,348 cases 2,462 controls	4 cases 2 controls	No
De Roos *et al.* (2003)	USA: Nebraska, Iowa, Minnesota, and Kansas	Nebraska: 1983-1986 Iowa: 1981-1983 Minnesota: 1980-1982 Kansas: 1979-1981	White males diagnosed with NHL in one of the 4 states (21 years or older in Nebraska and Kansas; 30 years or older in Iowa and Minnesota)	Males living in same geographic area obtained by random digit dialing, Medicare records and state mortality files - frequency matched for race, sex, age, and vital status	870 cases 2,569 controls	36 cases 61 controls	Yes (not significant in covariate analysis)
De Roos *et al.* (2005)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2001	Participants enrolled in AHS; licensed private and commercial applicators and spouses	Participants enrolled in AHS; licensed private and commercial applicators and spouses	54,315 subjects included in this analysis	All cancers – 358 cases Lung – 26 cases Oral cavity – 10 cases Colon – 15 cases Rectum – 14 cases Pancreas – 7 cases Kidney – 9 cases Bladder – 17 cases Prostate – 145 cases Melanoma – 14 cases All lymphohematopoietic cancers – 36 cases NHL – 17 cases Leukemia – 9 cases	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
						Multiple myeloma – 6 cases (13,280 subjects not exposed to glyphosate used for comparison population)	
Engel *et al.* (2005)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2000	Wives of applicators enrolled in AHS study with no history of breast cancer	Wives of applicators enrolled in AHS study with no history of breast cancer	309 cases 30,145 controls	82 cases; 10,016 controls	No
Eriksson *et al.* (2008)	Sweden	1999-2002	Patients (18-74 years of age) residing in Sweden and diagnosed with NHL	Swedish residents randomly selected living in same health service regions as cases - frequency matched for age (in 10 years) and sex	910 cases 1,016 controls	29 cases 18 controls	No
Flower *et al.* (2004)	USA: Iowa	1993-1997	Children (born after 1975) of participants enrolled in AHS study who were diagnosed with childhood cancer up to 19 years of age	Children (born after 1975) of participants enrolled in AHS study not diagnosed with childhood cancer up to 19 years of age	50 cases out of 17,357 total study population	Maternal use: 13 cases of 6075 total exposed Paternal use: 6 cases of 3231 total exposed	No
Hardell *et al.* (2002)	Sweden	NHL: 1987-1990 HCL: 1987-1992	NHL: Male residents of one of four northern or three middle counties in Sweden age 25 years and older diagnosed with NHL; identified from regional cancer registries HCL: Living male residents of Sweden age 25 years and older diagnosed with HCl; identified from the Swedish Cancer Registry	NHL: Two male controls for each case matched by age, year of death if deceased, and county HCL: Four male controls for each case matched by age and county	515 cases 1,141 controls	8 cases 8 controls	Yes (not evaluated)
Kachuri *et al.* (2013)	Canada: Alberta, British Columbia, Manitoba, Ontario,	1991–1994	Men aged ≥ 19 years (≥ 30 years in analysis) - pulled from hospital records in Quebec,	Men aged ≥ 19 years (30 years in analysis) - pulled from provincial health insurance records in	342 cases 1,357 controls	32 cases 121 controls	Yes (included in adjustment)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
	Quebec, and Saskatchewan		cancer registries in all other provinces	Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia			
Karunanayake *et al.* (2012)	Canada: Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	1991–1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	316 cases 1,506 controls	38 cases 133 controls	No
Koureas *et al.* (2014)	Greece	2010	Inhabitants of the city of Larissa; Eligibility criteria for pesticide sprayers were 1) to personally apply pesticides systematically, and 2) to have recently applied pesticides (no longer than 7 days between last application and sampling).	The rural residents group were occupied in administrative services, public order services, health services, education or trade. Inclusion criteria for this group: absence of any involvement in agricultural activities either as a primary or secondary occupation by participant or any member of household. Also recruited urban residents (mainly blood donors) from the city of Larissa.	80 pesticide sprayers, 85 rural residents, and 121 individuals	Not reported	No
Koutros *et al.* (2013)	USA: Iowa and North Carolina	Enrollment (1993-1997) through 2007	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	1,962 incident cases (including 919 aggressive prostate cancers) among 54,412 applicators	1464 cases 42,420 controls	No
Landgren *et al.* (2009)	USA: Iowa and North Carolina	Exposure information: enrollment (1993-1997) and 5-year follow-up interview	Males enrolled in AHS; licensed private and commercial applicators	Males enrolled in AHS; licensed private and commercial applicators	678 participants	27 cases out of 570 total exposed	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
		Blood samples: 2006-2007 (Iowa) and 2008 (North Carolina)					
Lee *et al.* (2004b)	USA: Nebraska	1988-1993	White residents of 1 of 66 Nebraska counties age 21 years or older with a newly confirmed case of adenocarcinoma of the stomach or Cases identified from the Nebraska Cancer Registry (1988–1990) or from discharge diagnosis and pathology records from 14 Nebraska hospitals (1991–1993)	Frequency matched by age and sex to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Health Care Financing Administration Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased)	Stomach: 170 cases Esophagus: 137 cases 502 Controls	12 cases 46 controls	Yes (analysis showed differences)
Lee *et al.* (2005)	USA: Nebraska	1988-1993	White residents of 1 of 66 Nebraska counties age 21 years or older with confirmed adult glioma. Cases identified from Nebraska Cancer Registry or from participating hospitals in Lincoln and Omaha, Nebraska	Frequency matched by age, sex, and vital status to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased), and 5-year age groups to the overall case distribution. Additional	251 glioma cases 498 controls	17 cases 32 controls	Yes (analysis showed differences, included in adjustment)

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
				younger controls were brought into the study through random digit dialing and from death certificates			
Lee *et al.* (2007)	USA: Iowa and North Carolina	1993-97; follow-up to 2002	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of colorectal cancer at enrollment. Followed through 2002 for incident colorectal cancer	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of colorectal cancer at enrollment. Followed through 2002 for incident colorectal cancer	56,813 licensed pesticide applicators 305 incident colorectal cancer cases (212 colon, 93 rectum) 56,508 controls	Colon - 151 cases; 49 controls Rectum - 74 cases; 18 controls Colorectal - 225 cases; 67 controls	No
McDuffie *et al.* (2001)	Canada: Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	1991-1994	Male residents of six Canadian provinces age 19 years and older diagnosed with STS, HD, NHL, or MM; this study only evaluated those with NHL. Cases were identified from Canadian Cancer Registries; in Quebec, hospital ascertainment was used	Random control subject selection using Health Insurance records, computerized telephone listings, and voters' lists; males 19 years and older from same six Canadian provinces as cases matched by age (within 2 years)	517 cases 1506 controls	Univariate analysis: 51 cases; 133 controls (multivariate analysis also conducted - glyphosate exposed numbers not reported)	No
Orsi *et al.* (2009)	France	2000-2004	Men aged 20–75 years living in the catchment areas of the main hospitals in Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux, with no history of immunosuppression or taking immunosuppressant drugs. Cases ascertained from hospital records.	Patients from the same hospital catchment area as the cases. Patients were hospitalized for orthopedic or rheumatological conditions (89.3%), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue disease (1.8%), and infections (3.0%), excluding patients admitted for cancer or a disease directly related to	491 cases 456 controls	NHL: 12 cases 24 controls HL: 6 cases 15 controls Lymphoproliferative syndromes: 4 cases 18 controls Multiple myeloma: 5 cases;18 controls Lymphoid neoplasms: 27 cases; 24 controls	No

Table C.1. Design Characteristics of Epidemiological Studies Evaluated for Study Quality.							
Study	**Location**	**Study Years**	**Case Population**	**Control Population**	**Total Number of Subjects**	**Number of Glyphosate Exposed Cases**	**Proxy Use**
				occupation, smoking, or alcohol abuse			
Pahwa *et al.* (2011)	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	1991-1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	342 cases 1,506 age/resident matched controls	32 cases 133 controls	No
Pahwa *et al.* (2012)	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	1991-1994	Men aged ≥ 19 years - pulled from hospital records in Quebec, cancer registries in all other provinces	Men aged ≥ 19 years - pulled from provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	342 cases 1506 age/resident matched controls	32 cases 133 controls	No
Yiin *et al.* (2012)	USA: Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	1995-1997	Age 18–80 (at ascertainment or diagnosis in 1995 through January 1997) residing in counties where the largest population center had fewer than 250,000 residents. Referral by physicians or through state cancer registries with cases verified by histological evaluation.	Controls age 18–64 randomly selected from state driver's license/nondriver ID records, and those age 65–80 were selected from Health Care Financing Administration's (HCFA) Medicare data within 10-year age group strata, with the proportion/stratum determined by the age distribution of glioma cases in that state from 1992 to 1994. Controls were frequency-matched within a state but not by county of residence. Selected even if they had a self-reported history of cancer other than glioma.	798 glioma cases; 1,175 controls	12 cases 19 controls	Yes (analysis showed no differences)

Appendix D. List of studies assigned a low quality ranking and not evaluated in detail

As described in Section 3.2, if studies did not collect exposure information on glyphosate from all subjects, did not assess an outcome (e.g., biomonitoring studies), and/or did not provide a quantitative measure of an association between glyphosate and a cancer outcome, then these studies were assigned a low quality ranking and were not further evaluated in detail. These studies included the following 32 studies:

Acquavella *et al.* 2006; Andre *et al.*, 2007; Baker *et al.* 2005; Benedetti *et al.*, 2013; Bolognesi *et al.*, 2002; Bolognesi *et al.*, 2004; Bolognesi *et al.* 2009; Bortoli *et al.*, 2009; Costa *et al.*, 2006; Da Silva *et al.* 2014; Dennis *et al.* 2010; Firth *et al.* 2007; Gomez-Arroyo *et al.*, 2013; Gregio D'Arce *et al.*, 2000; El-Zaemey *et al.*, 2013; Fortes *et al.*, 2016; Fritschi *et al.*, 2005; Hernandez *et al.,* 2006; Kaufman *et al.* 2009; Khayat *et al.*, 2013; Lebailly *et al.,* 2003; Mandel *et al.* 2005; Martinez-Valenzuela *et al.*, 2009; Monge *et al.*, 2007; Pastor *et al.*, 2003; Paz-y Mino *et al.,* 2007; Paz-y Mino *et al.* 2011; Ruder *et al.* 2004; Shaham *et al.*, 2001; Silva Kahl *et al.* 2016; Simoniello *et al.*, 2008; Vlastos *et al.,* 2006.

Appendix E

Chronic Dietary Exposure

The agency uses Dietary Exposure Evaluation Model- Food Consumption Intake Database (DEEM-FCID; version 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) to calculate potential chronic dietary exposures. In an unrefined chronic dietary analysis, several conservative assumptions are used to generate high end estimates of potential exposure. These assumptions include tolerance-level residues for all registered commodities, 100% crop treated, and drinking water values from a direct application to water scenario, as well as DEEM default processing factors. For glyphosate, the highest exposure value for any population subgroup in an unrefined chronic dietary analysis would be 0.23 mg/kg/day for children 1-2 years old (Table E.1; see T. Bloem, 30-NOV-2017, D429229 for DEEM inputs and results).

Table E.1. Chronic dietary exposure estimates

Population Subgroup	Exposure (mg/kg/day)
General U.S. Population	0.089771
All Infants (< 1 year old)	0.138338
Children 1-2 years old	**0.228379**
Children 3-5 years old	0.212036
Children 6-12 years old	0.147749
Youth 13-19 years old	0.088362
Adults 20-49 years old	0.074650
Adults 50-99 years old	0.061258
Females 13-49 years old	0.069318

Post-application Incidental Oral and Dermal Exposure

Glyphosate has residential uses, including application to turf, which would result in the highest potential post-application exposures; therefore, there is potential for children to be exposed via incidental oral and dermal routes from playing on treated lawns. For this assessment, the agency evaluates exposures from hand-to-mouth behavior, object-to-mouth behavior, incidental soil ingestion, and dermal contact using the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment[29]. Incidental oral exposures from hand-to-mouth, object-to-mouth, and incidental soil ingestion are considered inter-related and, therefore, not combined. To calculate high end estimates of exposures, the following is assumed according to the 2012 SOP to be health-protective: 1) maximum label rates are applied to the turf, 2) exposures are assumed to occur every day to the residue values on the day of application (i.e., no dissipation), and 3) individuals engage in post-application activities for the maximum amount of time represented by data for children spending time outdoors and not specifically engaged in activities

[29] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

on turf, when in actuality children do not spend all of their outdoor time on turf. The highest exposure from incidental oral scenarios using the maximum application rate for turf applications would be 0.16 mg/kg/day from hand-to-mouth behaviors by children (1 to <2 years old). Dermal post-application to children 1 to <2 years old would be 0.08 mg/kg/day.

Table E.2. Post-application Exposure Estimates for Application of Glyphosate to Turf[1].

Lifestage	Post-application Exposure Scenario		Exposure (mg/kg/day)
Children 1 to <2 year old	Turf – sprays	Hand-to-Mouth	0.16
		Object-to-Mouth	0.005
		Incidental Soil Ingestion	0.0003
		Dermal (high contact activities)	0.08

[1] Based on Roundup® Weed & Grass Super Concentrate, EPA Reg. No. 71995-25.

Appendix F

Genotoxicity Studies with Glyphosate Based Formulations

While the focus of this analysis to determine the genotoxic potential of glyphosate, the agency has identified numerous studies conducted with glyphosate-based formulations that contain various concentrations of the glyphosate as well as other components of the end use products and are presented in Tables F.1-F.5.

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98 and TA100; *E. coli* WP2 *uvrA* pKM101 ± S9	1.6-5000 µg/plate ± S9 (plate incorporation)	ICIA 0224 57.6% in water	Negative ± S9	Callander (1988)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537*; E. coli* WP2P and *uvrA* ± S9	100-5000 µg/plate ±S9 plate incorporation & pre-incubation protocols	TMSC (tri-methyl-sulfonium chloride) 95% purity	Negative ± S9	Callander (1993)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	26, 43, 72, 120, 200 µg/plate	Glyphosate liquid formulation (480 g/L isopropylamine salt)	Negative ± S9	Camolesi (2009)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	26, 43, 72, 120, 200 µg/plate	MON 77280 equivalent of glyphosate acid: 495 g/L	Negative ± S9	Camolesi (2010)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	0.2-2000 µg/plate	MON 76190 53.2% glyphosate	Negative ± S9	Catoyra (2009)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100 and TA102± S9	2 µg/plate (toxic)	Perzocyd 10 SL formulation	Negative ± S9	Chruscielska *et al.* (2000)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102,	0.03-3.0 µL/plate	MON 8080 (87.6%)	Negative ± S9	Flowers (1981)	

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
	TA1535, and TA1537 ± S9					
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	3.16-1000 µg/plate	TROP M (Glyphosate 480); 35.84% purity based on acid, 48.46% pure based on IPA salt	Negative ± S9	Flügge (2010a)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	0.316-100	Glyphosate 757 g/kg granular formulation (76.1% monoammonium glyphosate salt)	Negative ± S9	Flügge (2010d)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100, and TA1535 ± S9	1-5000 µg/plate	Roundup WG 784 g/kg ammonium salt equivalent	Negative ± S9	Gava (1998)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537± S9	50-5000 µg/plate	Rodeo® (containing IPA salt and water only); 40% glyphosate (acid equivalent)	Negative ± S9	Kier *et al.*, (1992)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 ± S9	5-500 µg/plate (-S9)/ 15-1500 µg/plate (+S9)	MON 2139 (Roundup®) 31% Glyphosate (acid equivalent)	Negative ± S9	Kier *et al.*, (1992)	Cytotoxic at top concentrations
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 ± S9	5-500 µg/plate (-S9)/ 15-1500 µg/plate (+S9)	MON 14445 (Direct®); 75% Glyphosate (acid equivalent)	Negative ± S9	Kier *et al.*, (1992)	Cytotoxic at the top concentrations, occasionally at lower concentrations
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 ± S9	0.2-2000 µg/plate	MON 79672 (Roundup Ultramax); 74.7% monoammonium	Negative ± S9	Lope (2008)[1]	

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
			glyphosate salt; 68.2% glyphosate			
Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 ± S9	0.617-50 µL/plate ± S9	SC-0224, 19.2% purity	Negative ± S9	Majeska (1982)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	TA strains: 10 - 5000 µg/plate (+S9); 3.33-3330 µg/plate (-S9); E. coli: 33.3-5000 µg/plate (+/- S9)	MON 78239 36.6% glyphosate (44.9% potassium salt of glyphosate)	Negative	Mecchi (2003a)	Increase in revertants seen in TA98 and TA1535 -S9 on first trial, not conc-dep; however no increase in revertants seen in repeat in those strains; overall negative.
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	TA strains: 3.33-3330 µg/plate (+S9); 1.0-1000 µg/plate (-S9); E. coli: 33.3-5000 µg/plate (+/- S9)	MON 78634 65.2% w/w glyphosate (71.8% w/w as monoammonium salt of glyphosate)	Negative	Mecchi (2003b)	
Bacterial Reverse Mutation	*S. typhimurium* TA 98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	10 - 5000 µg/plate (+/-S9)	MON 79864 38.7% glyphosate acid (wt %)	Negative	Mecchi (2008a)	Inhibited growth seen at ≥2000 -S9
Bacterial Reverse Mutation	*S. typhimurium* TA 98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	33.3-5000 µg/plate	MON 76313 30.9% glyphosate acid	Negative	Mecchi (2008b)	

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA 98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	10-5000 µg/plate (+/-S9)	MON 76171 31.1% glyphosate	Negative	Mecchi (2008c)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA 98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	10-5000 µg/plate (+/-S9)	MON 79991 71.6% glyphosate acid	Negative	Mecchi (2009a)	
Bacterial Reverse Mutation	*S. typhimurium* TA 98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* ± S9	10-5000 µg/plate (+/-S9)	MON 76138 38.5% glyphosate	Negative	Mecchi (2009b)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100, and TA1535 ± S9	1-5000 µg/plate	MON 77280 646.4 g/L salt equivalent	Negative	Perina (1998)	
Bacterial Reverse Mutation	*S. typhimurium* TA98 and TA100 ± S9	0-1440 µg/plate (calculated as glyphosate IPA salt)	Roundup, 480 g/L glyphosate isopropylamine salt	Negative – S9, Equivocal +S9	Rank *et al.* (1993)	Stat significant increase at 360 µg/plate for TA98 (-S9) and 720 µg/plate for TA100 (+S9). Not significant at higher concentrations and were not replicated. Effects occurred at close to toxic levels.

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	500-5000 µg/plate;	495 g/L glyphosate isopropylamine salt; 371.0 g/L (equivalent of glyphosate acid)	Negative ± S9	Silvino (2011)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	1.5-5000 µg/plate	MON 8709 495 g/L glyphosate isopropylamine salt; 371.0 g/L (equivalent of glyphosate acid)	Negative ± S9	Silvino (2011)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 ± S9	15-5000 µg/plate	MON 76313 468 g/L glyphosate isopropylamine salt (351 g/L glyphosate acid equivalent)	Negative ± S9	Silvino (2012)	Cytotoxic at 5000 µg/plate for some strains
Bacterial Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100 and TA1535 ± S9	1-5000 µg/plate	Glifos formulation (glyphosate isopropylammonium salt, Berol 907 and water)	Negative ± S9	Vargas (1996)	Cytotoxic at the two upper concentrations
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537± S9	3.16-316 µg/plate	FSG 3090-H1 360 g/L	Negative ± S9	Uhde (2004)[1]	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100 ± S9	0.01-100 µg/plate	64% (glyphosate Isopropylammonium salt)	Negative ± S9	Wang *et al.* (1993)	
Bacterial Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535,	All strains: 33.3-5000 µg/plate	MON 78910 30.3% glyphosate acid	Negative ± S9	Xu (2006)	Cytotoxic ≥1000 µg/plate (-S9)

Table F.1. *In vitro* Test for Gene Mutations in Bacteria: Glyphosate Formulations.						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
	TA1537 and *E. coli* WP2 *uvrA* ± S9	(+S9); 10-3330 µg/plate (-S9)				

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

Table F.2. *In Vitro* Tests for Chromosome Damage in Mammalian Cells- Glyphosate Formulations						
Test/Endpoint	**Test System**	**Concentrations**	**Test Material/ Concentration**	**Results**	**Reference**	**Comments**
***In vitro* Chromosomal Aberration using fluorescent in situ hybridization (FISH)**	Bovine lymphocytes (from two 6-8 month old calves) -whole chromosome (1) painting probe	28-1120 µM 24 h exposure	62% Isopropylamine salt of glyphosate (38% inert ingredients)	Negative.	Holeckova (2006)	Small but significant increase in polyploidy seen at 56µM No positive control reported.
***In vitro* Cytokinesis Block Micronucleus Assay (with FISH analysis)**	TR146 cells (human-derived buccal epithelial cell line)	0, 10, 15 and 20 mg/L; 20 minute exposure.	Roundup Ultra Max (450 g/l glyphosate acid)	Positive Increase in MN at all test concentrations	Koller *et al.* (2012)	No apoptosis observed at any conc. Necrosis reported at 20 mg/L. Increase in NB and NPB seen at all concentrations

MI= mitotic index. FISH= fluorescent in situ hybridization, MN= micronuclei; NB= nuclear buds; NPB= nucleoplasmic bridges.

Table F.3. *In Vivo* Tests for Chromosomal Aberrations in Mammals- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Chromosomal Aberration	Swiss albino mice (males only) Vehicle: DMSO	Intraperitoneal injection; sampling 24, 48 and 72 h	0, 25 and 50 mg/kg (5/dose)	Roundup (>41% isopropylamine glyphosate)	Positive Increase in MN at all time points at both doses	Prasad *et al.* (2009)	Significant decrease in mitotic index seen at all doses and time points
Bone Marrow Chromosomal Aberration	C57BL mice (males only) Vehicle: water	Oral administration; sampling 6, 24, 48, 72, 96 and 120 h	0.05, 0.01, 0.5 and 1.0% (8/dose)	Roundup	Negative	Dimitrov *et al.* (2006)	
Bone Marrow Chromosomal Aberration	New Zealand white rabbits (males only) Vehicle:	Drinking water for 60 days	0, 750 ppm (5/dose)	Roundup	Positive	Helal and Moussa (2005)	

BM= bone marrow, SC= spermatocyte.

Table F.4. *In Vivo* Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	Swiss CD1 mice (males only)	Intraperitoneal injection; 2 injections of half the dosage of 135 mg/kg 24 h apart; sampling at 6 and 24 h	0, 450 mg/kg roundup, equiv. to 135 kg glyphosate (3/dose)	Roundup, 30.4% glyphosate	Positive	Bolognesi *et al.* (1997)	Stat significant increase in MN at 6 and 24 h
Bone Marrow Micronucleus Test	C3H mice (males only) Vehicle: water	Intraperitoneal Injection (single treatment); sampling after 24, 48 and 72 h	0, 90 mg/kg	Not reported	Negative	Chruscielska *et al.* (2000)	
Bone Marrow Micronucleus Test	Swiss mice (males and females) Vehicle: water	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 50, 100 and 200 mg/kg	480g/L Isopropylamine salt of glyphosate	Negative	Grisolia (2002)	
Bone Marrow Micronucleus Test	CD-1 mice (males and females)	Intraperitoneal injection; sampling 24, 48 and 72 h	0, 140, 280, and 555 mg/kg	Roundup (31% glyphosate salt)	Negative	Kier (1992)	Some deaths observed at high dose (HD), ↓PCE/NCE ratio at HD at 48 h in males.
Bone Marrow Micronucleus Test	Swiss albino mice (males and females)	Intraperitoneal Injection (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 212.5, 425 and 637.5 mg/kg	MON 77280 646.4 g/L glyphosate salt equivalent	Negative	Monma (1998)	Doses tested corresponded to 25%, 50% and 75% LD50

Table F.4. *In Vivo* Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	NMRI-Bom mice	Intraperitoneal Injection (single treatment); sampling after 24 h	0, 133 and 200 mg/kg (4/sex/dose)	Roundup, 480 g glyphosate isopropylamine salt per liter	Negative	Rank *et al.* (1993)	BM toxicity indicated by %PCE decreased at 200 mg/kg
Bone Marrow Micronucleus Test	Swiss albino mice (males only[2]) Vehicle: water	Oral gavage (two treatments, 24 h apart); sampled at 18 and 24 h after last dose	0, 2000 mg/kg	MON 8709494.7 g/L salt of isopropylamine (371.0 glyphosate acid)	Negative	Claro (2011)	OECD 474 Guideline No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	C57BL mice (males only) Vehicle: water	Oral administration; sampling 6, 24, 48, 72, 96 and 120 h	0.05, 0.01, 0.5 and 1.0% (1%=1080 mg/kg) (8/dose)	Roundup	Negative	Dimitrov *et al.* (2006)	Toxicity seen in 1.0% dose group
Bone Marrow Micronucleus Test	Crl:CD-1(ICR) BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78239 (36.6% glyphosate)	Negative	Erexson (2003a)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Crl:CD-1(ICR) BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78634 (65.2% glyphosate)	Negative	Erexson (2003b)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Crl:CD-1(ICR) BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 78910 (30.3% glyphosate)	Negative	Erexson (2006)	EPA Guideline (84-2) No significant signs of toxicity observed in main study.

Table F.4. *In Vivo* Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.							
Test/Endpoint	**Test System**	**Route of Administration**	**Doses**	**Test Material Purity**	**Results**	**Reference**	**Comments**
Bone Marrow Micronucleus Test	NMRI mice (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	TROP M (Glyphosate 480); 358.4 g/L glyphosate acid; 483.6 g/L IPA salt	Negative	Flügge (2010c)[1]	OECD Guideline 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Swiss mice (males only[2]) Vehicle: water	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 2000 mg/kg (6/dose)	A17035A 289.7 g/L glyphosate	Negative	Negro Silva (2009)[1]	OECD Guideline 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Swiss mice (males only[2]) Vehicle: water	Oral gavage (2 treatments, 24 h apart); sampling after 24 h (last treatment)	0, 2000 mg/kg (6/dose)	Glyphosate SL (499.35 g/L glyphosate)	Negative	Negro Silva (2011)[1]	OECD Guideline 474 No significant signs of toxicity observed in main study
Bone Marrow Micronucleus Test	Hsd:CD-1(ICR) mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 79864 (38.7% glyphosate)	Negative #	Xu (2008a)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76171 (31.1% glyphosate)	Negative	Xu (2008b)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 79991 (71.6% glyphosate)	Negative	Xu (2009a)	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.

Table F.4. *In Vivo* Tests for Micronuclei Induction in Mammals- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses	Test Material Purity	Results	Reference	Comments
Bone Marrow Micronucleus Test	CD-1(ICR)BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76138 (38.5% glyphosate)	Negative	Xu (2009b)[1]	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	Hsd:CD-1(ICR)BR mice (males only[2]) Vehicle: water	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 (mg/kg) (5/dose)	MON 76313 (30.9% glyphosate)	Negative	Xu (2009c)[1]	EPA Guideline (84-2) /OECD 474 No significant signs of toxicity observed in main study.
Bone Marrow Micronucleus Test	CD rats (males and females) Vehicle: 0.8% hydroxypropylmethyl cellulose	Oral gavage (single treatment); sampling after 24 and 48 h (high dose only)	0, 500, 1000, and 2000 mg/kg (5/sex/dose)	757 g/kg granular formulation (69.1% glyphosate acid)	Negative	Flügge (2010e)[1]	OECD Guideline 474 No significant signs of toxicity observed in main study

[1] Study was cited in Kier and Kirkland (2013). Supplementary information about the study was provided online including test guideline, test material purity, control chemicals and summary data tables.

[2] Only males tested; report indicated that there was no difference between sexes seen in range finding study.

BM= bone marrow, CA= chromosomal aberrations, MN= micronucleated erythrocytes, NCE= normochromatic erythrocytes, PCE=polychromatic erythrocytes.

Table F.5. Other Assays for Detecting DNA Damage- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material/ Concentration	Results	Reference	Comments
Bacterial SOS Chromotest	*Escherichia coli* PQ37 strain	NA (*in vitro*)	0.25µg/sample	Roundup BIO formulation;	Positive	Raipulis *et al.* (2009)	
DNA Adducts ^{32}P-postlabeling	Swiss CD1 mice (males and females) Liver and kidney evaluated	Intraperitoneal injection	0, 400, 500 and 600 mg/kg, corresponding to 122, 152 and 182 mg/kg glyphosate salt	Roundup (30.4% isopropylammonium salt of glyphosate)	Positive (liver and kidney)	Peluso *et al.* (1998)	
DNA oxidative damage: 8-OHdG formation	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	900 mg/kg corresponding to 270 mg/kg glyphosate (3/dose)	900 mg/kg corresponding to 270 mg/kg glyphosate	Kidney: positive at 8 and 24 h Liver: negative	Bolognesi *et al.* (1997)	
Single-cell gel electrophoresis (SCGE) assays-COMET assay	TR146 cells (human-derived buccal epithelial cell line). Alkaline conditions	NA (*in vitro*)		Roundup Ultra Max (450 g/l glyphosate acid)	Induced DNA migration at >20 mg/L	Koller *et al.* (2012)	Also measured multiple cellular integrity parameters to assess cytotoxicity. Formulation was more toxic than technical. Significant increase in LDHe at all concentrations tested. Cytotoxic ≥ 60 mg/L
Sister Chromatid Exchange (SCE)	Bovine lymphocytes	NA (*in vitro*)	28 - 1112 µM; ±S9; sampling at 24 and 48 h	62% Isopropylamine salt of glyphosate	Positive	Sivikova & Dianovsky (2006)	

Table F.5. Other Assays for Detecting DNA Damage- Glyphosate Formulations.

Test/Endpoint	Test System	Route of Administration	Doses/ Concentrations	Test Material/ Concentration	Results	Reference	Comments
Sister Chromatid Exchange (SCE)	Human lymphocytes (2 donors)	NA (*in vitro*)	250, 2500 and 25000 µg/mL	Roundup; Isopropylamine salt of glyphosate (purity not stated)	Stat. significant increase ($p<0.001$) at 250 µg/mL in both donors, and in one donor at 2500 µg/mL	Vigfusson and Vyse (1980)	No growth seen at highest concentration (25 mg/mL)
Sister Chromatid Exchange (SCE)	Human lymphocytes	NA (*in vitro*)	-S9: 0, 0.1 and 0.33 mg/mL; 72 h exposure	Roundup, 30.4% glyphosate	Positive	Bolognesi *et al.* (1997)	Stat significant increase in SCE/cell at ≥ 0.1 mg/mL
Alkaline elution assay- DNA single strand breaks	Swiss CD-1 mice (males) liver and kidney evaluated	Intraperitoneal injection (single dose); sampling 4 and 24 h after injection	900 mg/kg corresponding to 270 mg/kg glyphosate (3/dose)	900 mg/kg corresponding to 270 mg/kg glyphosate	Positive (Increased elution rate) at 4 hours in liver and kidney At 24 h, returned to control levels	Bolognesi *et al.* (1997)	Return to control values at 24 h may indicate DNA repair or reflect rapid elimination of compound

h= hour, NA= not applicable, SCE= sister chromatid exchange, LDHe= extracellular lactate dehydrogenase

Appendix G

The following studies were considered during the systematic review, but were excluded from the analysis.

Amer S.M. et al (2006). In vitro and in vivo evaluation of the genotoxicity of the herbicide glyphosate in mice. Bulletin of the National Research Centre (Cairo) 31 (5): 427-446.

Aboukila, R.S. *et al*. (2014). Cytogenetic Study on the Effect of Bentazon and Glyphosate Herbicide on Mice. Alexandria Journal of Veterinary Sciences, 41: 95-101.

Majeska (1982d) MRID 00126616

Majeska (1982e) MRID 00126614

Majeska (1982f) MRID 00126615