Appendix L. Health and Safety Risks to the General Population

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Health and Safety Risks to the General Population

Executive Summary

In an effort to assess the potential health and safety risks to humans from increased glyphosate and other chemical use in agriculture (exclusive of field workers) due to the deregulation of glyphosate-tolerant alfalfa by the U.S. Department of Agriculture (USDA) in 2005, a screening-level human health risk and safety assessment was conducted for glyphosate use on glyphosate-tolerant (GT) alfalfa. Because ingestion of alfalfa is low, risk was assessed assuming fruits and vegetables were sprayed in error. For other potential health concerns from GT alfalfa, including worker and livestock exposure to glyphosate, see section IV.E and appendices M and Q.

As defined by EPA, screening-level risk assessments "are conservative assessments in that they provide a high level of confidence in determining a low probability of adverse risk, and they incorporate uncertainty in a precautionary manner" and "are not designed nor intended to provide definitive estimates of actual risk" (U.S. EPA, 2001). Rather, the purpose of screening-level risk assessments is to assess the need to conduct a detailed risk assessment (EPA, 2001a). By definition, the Animal and Plant Health Inspection Service (APHIS) recognizes that the Preferred Alternative and Isolation/Geographic Restriction Alternative are unlikely to have any adverse impacts that might be indicated by the results of the assessment, and the assessment is intended to disclose very conservative potential impacts. Screening-level hazard estimates suggest that the general population is not at risk for adverse health effects associated with acute or chronic exposure to glyphosate. More details on the toxicity and risk of glyphosate are discussed in this technical report.

It is unknown to what extent, if any, the general public could be exposed to herbicides used on GT alfalfa if they consume crops that were grown near GT alfalfa fields or animal commodities arising from livestock fed on intentionally or unintentionally treated alfalfa. Given the expected increase in glyphosate use that would result from deregulation, a screening-level human health risk assessment for the general population was conducted using highly conservative assumptions.

To conduct the screening-level risk assessment, high-end estimates of exposure are compared with a health benchmark specific to glyphosate. USDA (2003) used a chronic (long term) reference dose (RfD) for glyphosate of 2 mg per kg of body weight per day to assess both acute (i.e., short term or accidental) and chronic (i.e., long term) exposure scenarios. This means that individuals with exposure doses equal to or less than 2 mg per kg of body weight per day are not at risk of adverse effects associated with exposure to glyphosate. The risk metric that is used to characterize risk of adverse effects is called the hazard quotient (HQ). The HQ is the ratio of the estimated exposure dose to the chemical-specific health benchmark (e.g., RfD).

If the HQ is estimated to be less than 1—or given the screening level nature of the assessment at or even somewhat above 1—no adverse effects are expected as a result of exposure to the chemical of concern. If the HQ is much greater than 1, adverse health effects are possible. As noted above, the nature of this screening-level risk assessment precludes any conclusions regarding the likelihood of adverse health effects.

Most of the screening level HQs are under 1. Some upper estimate screening HQs do exceed 1, but are based on very conservative assumptions for estimates of exposure and, for acute assessment, are based on the highly conservative assumption of a chronic RfD for acute toxicity. Acute oral exposure estimates from fruit ingestion for adults ranged from zero to 1.25 mg/kg bw/day. For elderly people, acute oral exposure estimates from fruit ingestion ranged from 0.0125 to 0.45 mg/kg bw/day. For infants, acute oral exposure estimates from fruit ingestion ranged from zero to 6.32 mg/kg bodyweight per day. Acute oral exposure estimates from vegetable ingestion for adults ranged from 0.185 to 4.61 mg/kg bw/day. For elderly people, acute oral exposure estimates from vegetable ingestion ranged from 0.222 to 5.11 mg/kg bw/day. For infants, acute oral exposure estimates from vegetable ingestion ranged from 0 to 12.1 mg/kg bw/day.

Central and lower screening HQ estimates were all less than 1. The age group at highest risk is infants under one year of age, which is consistent with the EPA findings (U.S. EPA, 2006, 1993). The upper estimate screening HQ for infants with acute exposure to fruit was approximately 3. The upper estimate screening HQs for all age groups with acute exposure to vegetables ranged from approximately 2 to 6. Due to the screening level nature of this assessment, APHIS believes that the actual result in HQs from the implementation of the Preferred Alternative or Isolation/Geographic Restriction Alternative would be less than 1. The upper estimates of risk are based on highly conservative fruit and vegetable intake rates and a high estimate of glyphosate residue concentrations. Furthermore, the use of a chronic toxicity RfD for assessing acute toxicity is also conservative given (1) acute RfDs typically are much higher—usually by more than an order of magnitude—than chronic RfDs, and (2) EPA has concluded that that no relevant toxic effects are expected to result from single-dose oral exposure to glyphosate.

Chronic oral exposure estimates from fruit ingestion for adults ranged from 0 to 0.683 mg/kg bw/day. For elderly people, chronic oral exposure estimates from fruit ingestion ranged from 0.00682 to 0.246 mg/kg bw/day. For infants, chronic oral exposure estimates from fruit ingestion ranged from 0 to 3.46 mg/kg bw/day. Chronic oral exposure estimates from vegetable ingestion for adults ranged from 0.101 to 2.52 mg/kg bw/day. For elderly people, chronic oral exposure estimates from vegetable ingestion ranged from 0.122 to 2.80 mg/kg bw/day. For infants, chronic oral exposure estimates from vegetable ingestion ranged from zero to 6.65 mg/kg bw/day.

Central and lower screening HQ estimates were all less than 1. Some of the upper estimate screening HQs do exceed 1, but these are based on the very conservative assumptions for estimates of exposure and, for the acute assessment, are based on the highly conservative assumption of a chronic RfD for acute toxicity. The age group at highest risk again is infants under one year of age, which is consistent with the EPA findings (1993, 2006). The upper estimate screening HQ for infants with chronic exposure to fruit was approximately 2. The upper estimate screening HQs for all age groups with chronic exposure to vegetables ranged from approximately 1 to 3. Due to the screening level nature of this assessment, APHIS believes that the actual result in HQs from the implementation of the Preferred Alternative or Isolation/Geographic Restriction Alternative would be less than 1. The upper estimates of risk are based on highly conservative fruit and vegetable intake rates and a high estimate of glyphosate residue concentrations.

1.0 Introduction

1.1 Background

In June 2005, the USDA approved the use of Roundup Ready® alfalfa, the only commercially available genetically engineered alfalfa on the market. The Monsanto Company (Monsanto) produced this GT alfalfa variety in partnership with the largest alfalfa seed company, Forage Genetics International. This genetically engineered alfalfa is resistant to the herbicide glyphosate (i.e., the alfalfa is able to survive applications of herbicides containing glyphosate), the active ingredient in the Monsanto Company's trademark herbicide, Roundup®. The transgene responsible for glyphosate resistance was first introduced into soybeans in 1996, and has been commercialized in several other crops (e.g., corn, canola, and cotton) since then. Alfalfa is the first perennial GT crop that was approved for commercial planting in the United States. In 2005 when GT alfalfa was introduced commercially, only 0.2 percent of the total harvested alfalfa was GT alfalfa; however, in 2006, three million pounds of seed was made available for planting (Gianessi and Reigner, 2006).

Glyphosate was first introduced as an herbicide under the trade name of Roundup® by Monsanto in 1974. Glyphosate is a nonselective herbicide registered for use on many food and nonfood field crops as well as noncrop areas where total vegetation control is desired. Glyphosate is among the most widely used pesticides by volume (U.S. EPA, 1993). Glyphosate use increased more than six-fold between 1992 and 2002, to become the most used herbicide in the United States, in most part due to approval of several GT crops (Gianessi and Reigner, 2006). In 1997, it was listed on the Agency of Toxic Substances and Disease Registry's 100 most frequently released substances (ATSDR, 1997).

As described in detail in appendix J, *Effects of Changes in Farming Practices on Water, Soil, and Air Due to Use of Glyphosate-Tolerant Alfalfa*, the deregulation of GT alfalfa will probably change alfalfa herbicide use profiles. Glyphosate use likely has increased as a result of GT crops, but some uncertainty exists regarding whether other (more toxic and/or persistent) herbicides have increased or decreased as a result of GT crops or will in the future. A few studies have claimed that the volume of herbicide use is greater due to GT crops (Benbrook, 2004, 2003, 2001). On the other hand, others, such as Heimlich et al. (2000) have indicated there has not been a significant increase in the amount of glyphosate use since emergence of GT crops. Heimlich et al. (2000) noted that using glyphosate has resulted in the replacement of herbicides that are at least three times as toxic and persist almost twice as long as glyphosate. For example, in cotton and soybeans fields, for the most part, several herbicides were replaced by glyphosate (million pounds reduction): bentazon (-4.4), disodium methanearsenate (-0.8), fluometuron (-4.5), imazethapyr (-1.0), metribuzin (-1.5), methylarsonic acid sodium salt (MSMA) (-1.7), paraquat (-2.9), pendimethalin (-14.0), sethoxydim (-1.1), and trifluralin (-13.0). Furthermore, prior to 2002, metolachlor, which accounted for 67 million pounds of herbicide used in 1997, was voluntarily withdrawn from the market prior to 2002; R/S Metolachlor was voluntarily cancelled, but S-Metolachlor replaced it on the market. Glyphosate was adopted on many soybean acres that were previously treated with metolachlor. Cyanazine, which accounted for 20 million pounds of herbicide used in 1997, was also voluntarily withdrawn from the market

prior to 2002 and replaced by glyphosate for use on cotton and corn. In addition to glyphosate, corn producers replaced cyanazine with the herbicides mesotrione, rimsulfuron, and simazine (Gianessi and Reigner, 2006).

Additionally, Trewavas and Leaver (2001) conducted an analysis which revealed that 3.27 million kg of other herbicides have been replaced with 2.45 million kg of glyphosate in soybean fields in the United States. Carpenter and Gianessi (2003) concluded that the introduction of GT soybeans has resulted in a decrease in the total volume of herbicides used. Gianessi (2005) estimates that averaged over all GT crops, GT technology has reduced herbicide use by 17 million kg/year in the United States. However, Gianessi's (2005) calculations indicate that if GT sugarbeets were adopted, reduction in herbicide use would not be as great as for combined GT crops, because the herbicides used now in nontransgenic sugarbeets are mainly low use rate compounds in the United States.

Given the expected increase in glyphosate use that would result from deregulation, a screening-level human health risk assessment for the general population was conducted using a combination of highly conservative assumptions. As defined by EPA, screening-level risk assessments "are conservative assessments in that they provide a high level of confidence in determining a low probability of adverse risk, and they incorporate uncertainty in a precautionary manner" and "are not designed nor intended to provide definitive estimates of actual risk" (U.S. EPA, 2001). Rather, EPA notes, the purpose is to assess the need to conduct a more detailed and precise risk assessment. Due to the screening level nature of this assessment, APHIS believes that the results should not be construed as indicating the likelihood of actual adverse health effects. Not only are the assumptions used in this assessment purposely conservative, but enforceable pesticide tolerances have been put in place to prevent excessive exposure.

1.2 Methodology

In the preparation of this human health risk assessment, literature searches on glyphosate toxicity and exposure were conducted in the open literature using the literature search strategy presented in appendix L-2 of this technical report. This human health risk assessment is not a comprehensive summary of all of the available information and does not cite all of the available literature. As USDA determined in 2003, an all inclusive and detailed review of each study would tend to obscure rather than inform. Therefore this document relies on the information that is likely to impact the risk assessment. Primary sources of data were obtained from the following three documents: the EPA 1993 Reregistration Eligibility Decision (RED) document on glyphosate (U.S. EPA, 1993); the EPA Glyphosate Human Health Risk Assessment for Proposed Use on Indian Mulberry and Amended Use on Pea, Dry (U.S. EPA, 2006); and the USDA, Forest Service 2003 human health and ecological risk assessment on glyphosate (USDA, 2003). However, several DIALOG databases were searched, and Google and Google Scholar search engines supplemented the DIALOG search. References were selected from the extensive list of literature based on requesting the abstracts and determining if the open literature data were not included in the three primary documents listed below or provided contrary or controversial information to these documents.

Additionally, for the exposure assessment, the application rate of glyphosate on GT alfalfa was determined by reviewing the five glyphosate herbicide formulations that are labeled for use on GT alfalfa and report the maximum daily and yearly use rate on GT alfalfa. These formulations are all Monsanto Company products, as GT alfalfa is also a Monsanto product. To develop the quantitative risk assessment the maximum use rate was determined to be 1.99 lb a.i./acre for a single use (rounded to 2 lb a.i./acre in calculations), with minimum reapplication within seven days and not to exceed 7.3 lb a.i./acre in a year. The maximum label rate for a single ground use of Roundup® products used on GT alfalfa is 1.90 lb a.i./acre. Thus, the risk assessment is a conservative one. Furthermore, it should be noted that in this technical report, the term a.e. refers to the weight of the glyphosate acid, which is herbicidal, while the term a.i. is the weight of the glyphosate acid plus the salt.

2.0 Overview of Glyphosate

2.1 Glyphosate

Glyphosate is a systemic, post-emergence herbicide widely used on agricultural commodities (food uses) and nonagriculture sites. Glyphosate salts serve as the source of *N*-(phosphonomethyl)-glycine. Several salts of glyphosate with different counter cations are currently marketed. Each salt has a different "glyphosate equivalent", which is defined as the ratio of the molecular weight of *N*-(phosphonomethyl)-glycine to the molecular weight of the salt. While GT alfalfa could tolerate other herbicides formulated with glyphosate, only certain glyphosate herbicides are approved for use on GT alfalfa. The five currently approved glyphosate-containing herbicides are presented in table L-1. For the remainder of this report, these products will be referred to simply as glyphosate formulations.

Table L-1. End Use Products Approved for Use on Glyphosate-Tolerant Alfalfa

Product Name	% Salt	Glyphosate salt CAS No.	EPA PC Code	Surfactant	Manufacture
Honcho®	41	Isopropylamine CAS: 38641-94-0	103601	Alkyl Tallow Ethoxylated Amines CAS 61791-26-2	Monsanto, 2007a
Honcho Plus®	41	Isopropylamine CAS: 38641-94-0	103601	Trade Secret	Monsanto, 2007b
Roundup Original MAX®	48.7	Potassium CAS: 70901-12-1	103613	Trade Secret	Monsanto, 2007c
Roundup WeatherMAX®	48.8	Potassium CAS: 70901-12-1	103613	Trade Secret	Monsanto, 2007d
Roundup Ultra MAX II®	48.8	Potassium CAS: 70901-12-1	103613	Trade Secret	Monsanto, 2004

Structure and Nomenclature

Glyphosate is a substituted glycine, the simplest amino acid. The glyphosate molecule has a methylphosphono group bonded to the nitrogen atom of the amino group of glycine as denoted in figure L-1 below.

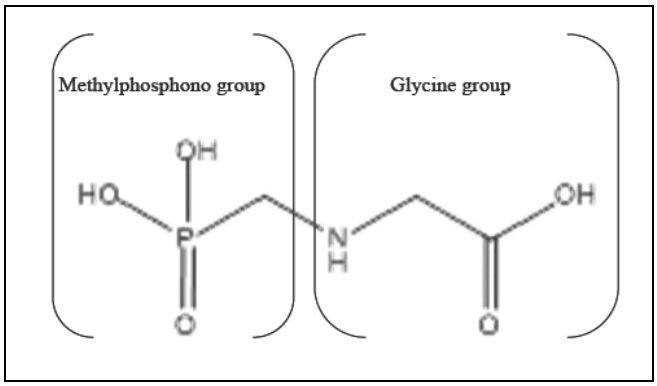

Figure L-1: Glyphosate molecular structure

Glyphosate's structure and nomenclature are presented in table L-2 below.

Table L-2. Glyphosate Structure and Nomenclature

Property	Value	Source
Common Name	Glyphosate	U.S. EPA, 2006; 1993
International Union of Pure and Applied Chemistry Name	*N*-(phosphonomethyl)glycine	U.S. EPA, 2006; 1993
Chemical Abstract Registry Number	1071-83-6	U.S. EPA, 1993
Empirical Formula	C3H8NO5P	U.S. EPA, 2006
Smiles notation	OC(=O)CNCP(O)(O)=O	U.S. EPA, no date
PC Code	417300	U.S. EPA, 1993

2.1.2 Physical and Chemical Properties

Physical and chemical properties of glyphosate are in table L-3 below.

Table L-3. Physical and Chemical Properties of Glyphosate

Property	Value	Source
Molecular Weight g	169.07	USDA, 2003
Density at 25°C	1.7	U.S. EPA, 1993
Solubility in water at 25°C	12,000 mg/L	U.S. EPA, 1993
pKa	0.8 first phosphonic acid 2.3 carboxylate 6.0 second phosphonic acid 11.0 amine	
Vapor Pressure at 25°C, Pa	1.3×10^{-7}	U.S. EPA, 1993
Henry's Law Constant (Pa m^3/mol)	2.1×10^{-9}	U.S. EPA, 1993
Log Kow	-3	U.S. EPA, 1993
Hydrolysis	Stable ≥30 days at pH 3, 6, and 9 at 5 and 35°C	U.S. EPA, 1993
Photolysis	Does not absorb light energy pH 5, 7, and 9	U.S. EPA, 1993
Metabolism in soil, half life	1.85 – 2.06 day	U.S. EPA, 1993
Metabolism water-sediment system, half life	Aerobic: 7 days Anaerobic: 8.1 – 199 days	U.S. EPA, 1993
Soil Mobility, $K_{ads\ Freundlich}$	9.4 – 700 mL/g	U.S. EPA, 1993
Soil water partition coefficient $K_{d\ (adsorption)}$	62 Drummer silty clay loam 90 Ray silt 70 Spinks sandy loam 22 Lintonia sandy loam 175 Cattail swamp sediment	U.S. EPA, 1993
Soil adsorption K_{oc}	2100 (500 – 2600) (L/kg) 2600 – 4900 (L/kg) 8 to >500,000 (L/kg) 54 (L/kg)	USDA, 2003
Metabolite	aminomethyl phosphonic acid (AMPA)	U.S. EPA, 1993
Field dissipation (application rate: 7.95 lb a.e./acre, 10.7 lb a.i./acre), half life	13.9 days (median) 2.6 days in Texas 140.6 days Iowa	U.S. EPA, 1993
Aquatic field dissipation, half life	7.5 days and 120 days	U.S. EPA, 1993
Bioaccumulation in fish	0.38X edible tissue 0.63X nonedible tissue 0.52X whole fish	U.S. EPA, 1993

2.2 Summary of Findings

Glyphosate is a systemic, post-emergence herbicide widely used on both agricultural commodities (food uses) and nonagriculture sites. Glyphosate salts serve as the source of the a.i. *N*-(phosphonomethyl)glycine. Several salts of glyphosate with different counter cations are currently marketed. At ambient temperatures, glyphosate is a white crystalline substance that is not volatile with high water solubility. In the crystalline form, glyphosate has both positive and negative regions of charge. These dipolar ion species are sometimes referred to as a zwitterion. In aqueous solutions, the hydrogen atoms of the carboxylic acid (COOH) and phosphate (PO_4H_2) groups could be associated or dissociated depending on the pH of the solution. These dipolar ion species are the regions expected to bond to carbon containing molecules in the soil. Glyphosate is in a liquid form for herbicide formulations; generally, the composition of the herbicide is considered a trade secret. One formulation of glyphosate, Honcho®, has a tallow amine surfactant (Monsanto, 2007a). This and other surfactants are added to the herbicide formulations to increase leaf penetration.

3.0 Human Health Risk Assessment

3.1 Hazard Identification

This general public risk assessment focuses on risks associated with exposure to herbicides recommended for use on GT alfalfa, all of which contain the active ingredient glyphosate. The risk assessment is presented in four sections including a hazard identification section in which toxicological data on glyphosate are reviewed and summarized, an exposure assessment section, in which exposure estimates for the general public are presented, a dose-response assessment section, in which health benchmarks for glyphosate are reviewed and recommended for different exposure scenarios, and, finally, a risk characterization section, in which exposure estimates are compared to health benchmarks to determine the potential for adverse health effects associated with general exposures to glyphosate.

3.1.1 Overview

According to EPA, the existing toxicity database for glyphosate is complete and without data gaps. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment (U.S. EPA, 2006, 1993). EPA considers glyphosate to be of low acute toxicity by oral, dermal, and ocular routes of exposure, since all studies are classified as Toxicity Category III (slightly toxic) or IV (practically nontoxic). Furthermore, an acute inhalation study was waived by EPA because glyphosate is a nonvolatile solid and the studies conducted on its end-use product (EUP) formulations are considered sufficient (U.S. EPA, 2006, 1993). In general, the herbicidal activity of glyphosate is due primarily to a metabolic pathway that does not occur in humans or other animals, and, thus, this mechanism of action is not directly relevant to the human health risk assessment.

In terms of subchronic and chronic toxicity, one of the more consistent effects of exposure to glyphosate is reduced body weight gain (several species). Other general and nonspecific signs of toxicity from subchronic and chronic exposure to glyphosate include changes in liver weight, blood chemistry (could suggest mild liver toxicity), and in liver pathology (USDA, 2003). Glyphosate is not a carcinogen and has been classified by EPA as a Group E carcinogen (evidence of noncarcinogenicity for humans) (U.S. EPA, 2006, 1993). Glyphosate's toxicity database and its mechanism of action are discussed in greater detail in the following sections. Additionally, a summary table of the toxicology studies included in the USDA (2003) and EPA (1993) documents is included in appendix L-3 of this technical report.

3.1.2 Mechanisms of Action

In plants, glyphosate is a potent and specific inhibitor of the enzyme 5-enolpyruvylshikimate 3-phosphate synthase (ESPS) in plants. ESPS is the sixth enzyme on the shikimate pathway and it is essential for the biosynthesis of aromatic amino acids and other aromatic compounds in algae, higher plants, bacteria, fungi, and apicomplexian parasites. However, this metabolic pathway does not exist in humans or other animals (USDA, 2003; U.S. EPA, 1993).

While its mechanism of action in plants is well understood, not as much is known about glyphosate's ability to cause toxic effects in humans or experimental animals, based on acute oral exposure by ingesting raw agricultural product. Corrosive effects on the gastric mucosa, as well as other tissues, are a consistent response following acute oral exposure to high doses of glyphosate or polyethoxylated tallow amine (POEA), a surfactant included in some glyphosate formulations. However, it is speculated that the biochemical pathway leading to mucosal effects differs for each glyphosate and POEA. At present, two biochemical mechanisms of action for glyphosate are proposed in humans: uncoupling of oxidative phosphorylation and inhibition of hepatic mixed function oxidases (USDA, 2003).

Oxidative phosphorylation is a process where nutrients are oxidized to yield metabolic energy which is then transferred to high-energy phosphate bonds and stored. Glyphosate appears to be an uncoupler of oxidative phosphorylation based on the results of a series of experiments using rat liver mitochondria that was exposed to glyphosate (USDA, 2003). When a substance uncouples this process, the result is a loss of energy and eventually death. Symptoms such as increased heart and respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis, and weight loss could occur in response to the uncoupling of oxidative phosphorylation. Uncoupling of this process has been seen after experimental animals were given intraperitoneal doses as low as 15 mg/kg. However, it has not been determined if uncoupling of oxidative phosphorylation plays a major role in glyphosate acute exposures (USDA, 2003).

Inhibition of hepatic mixed-function oxidases might also account for some of the toxic effects observed following glyphosate exposure. Hepatic mixed-function enzymes are comprised of various isozymes of cytochrome P-450, which is involved in the metabolism of a variety of endogenous compounds as well as xenobiotics. In a study by Hietanen et al. (1983), a decrease in hepatic mixed-function oxidase activity was observed in rats after a 500 mg/kg/day dose of glyphosate for four days followed by doses of 300 mg/kg/day for six days. While this decrease in hepatic mixed-function oxidase activity is only indicative of cytochrome P-450 inhibition, it has been suggested that this effect might be due to glyphosate's inhibition of cytochrome P-450, since glyphosate has caused inhibition in plants (USDA, 2003).

3.1.3 Kinetics and Metabolism

The residue of concern for risk assessment purposes is glyphosate *per se*. Glyphosate's only known metabolite, (aminomethyl)phosphonic acid (AMPA; see figure L-2), is not included in either the tolerance expression or the risk assessment (U.S. EPA, 2006). While AMPA is a common environmental metabolite, only trace amounts of it are formed in mammals, with the remainder of the glyphosate being excreted unchanged. For this reason, direct exposures to AMPA, as an endogenous metabolite in animals, are encompassed by the existing toxicity data on glyphosate.

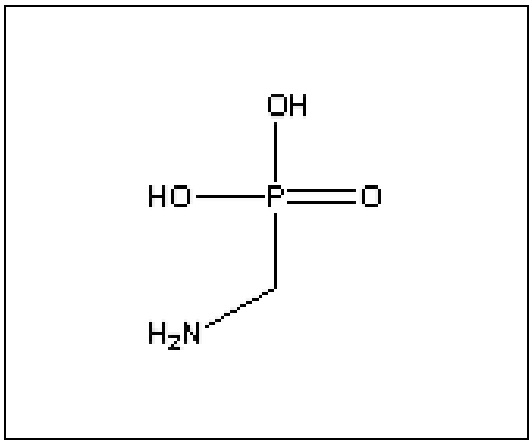

Figure L-2: Chemical structure of AMPA

Since glyphosate is rapidly eliminated from the body and shows a lack of degradation into toxic metabolites, dose levels expressed in mg/kg/day display analogous effects over broad periods of exposure (USDA, 2003). For the general public, the majority of exposures to glyphosate are via the oral and dermal route. Select results from both oral and dermal absorption studies are discussed below.

According to experimental studies, glyphosate is not completely absorbed following oral administration. Much of the reviewed literature has revealed that only about 30 percent of glyphosate is absorbed from the gastrointestinal tract after oral exposure (USDA, 2003). One metabolism study available at the time of the 1993 reregistration of glyphosate involved a single or repeated dose of radiolabeled ^{14}C-glyphosate administered orally to Sprague-Dawley rats. Of this dose, 30-36 percent was absorbed, <0.27 percent was eliminated as CO_2, 97.5 percent was excreted in the urine and feces as parent compound, and 0.4-0.7 percent was excreted in the urine and feces as AMPA. Repeated dosing did not significantly change the metabolism (U.S. EPA, 1993).

Furthermore, studies conducted by Davies (1996e), indicate that the majority of unabsorbed glyphosate remains in the gastrointestinal tract, while the absorbed glyphosate is widely distributed throughout the body. The highest concentrations of glyphosate are found in the bone (<1 percent of dose) relative to other tissues, although glyphosate does not significantly concentrate or persist in any tissue (U.S. EPA, 1993). A second metabolism study available at the time of the 1993 reregistration of glyphosate involved dosing Sprague-Dawley rats with a single 1150 mg/kg intraperitoneal injection of radiolabeled ^{14}C-glyphosate. Approximately 0.0044-0.0072 percent of this dose was found in the bone marrow after 30 minutes. The half-life of glyphosate in bone marrow was 7.6 hours for males and 4.2 hours for females. In addition, the study determined that the half life of glyphosate in plasma was 1 hour for both sexes (U.S. EPA, 1993).

Glyphosate is also poorly absorbed following dermal applications, as indicated by two dermal absorption studies performed by Wester et al. (1991, 1996). One of the studies was performed using skin from human cadavers. In this study, the cadaver skin was exposed to an undiluted glyphosate herbicide formulation (i.e., Roundup®) for eight hours and diluted formulations (i.e., 1:20 and 1:32 dilutions of Roundup®) for up to 16 hours. In general, formulations generally

contain more of the POEA surfactant than the active ingredient, glyphosate. Based on 16-hours of exposure to the diluted formulations, first-order dermal absorption rates ranged from $1.3x10^{-4}$ to $1.0x10^{-3}$ h^{-1} (average: $4.1x10^{-4}$ h^{-1}), while first-order dermal absorption rates after 8-hours of exposure to the more concentrated formulation ranged from $7.5x10^{-5}$ to $5.1x10^{-4}$ (USDA, 2003). The results of this study indicated that glyphosate containing more of the POEA surfactant (i.e., the undiluted formulation) did not absorb more rapidly than a glyphosate formulation with a less concentrated solution of surfactant. A second study was performed on monkeys and found that after 12 hours of exposure approximately 1.5 percent of the glyphosate was absorbed, which is equivalent to a first-order dermal absorption rate of $1.3x10^{-3}$ $hour^{-1}$ (Wester, 1991). Wester's dermal absorption rates are used later in the occupational exposure assessment. Wester's experimental measurements and methods are consistent with other derived values and standard methods used to estimate first-order dermal absorption rates (USDA, 2003)

3.1.4 Acute Systemic Toxicology

As is common with most chemicals, acute exposure to glyphosate and its commercial formulation could be toxic at sufficiently high levels. For example, an experiment performed by Williams et al. (2000) on rats and mice found that acute oral LD_{50} values (the lethal dosage required to kill 50 percent of a population of test animals) of glyphosate range from approximately 2,000 to 6,000 mg/kg and acute oral intraperitoneal LD_{50} values, which are about 10 times lower in value, range from 134 to 234 mg/kg (USDA, 2003). Additionally, systemic differences in toxicity do not appear to exist among species when doses of glyphosate are expressed in units of mg/kg body weight.

Documentation suggests that exposure to glyphosate with a POEA surfactant is a common means of suicide, and this fact can be used to make a determination about its effects on humans. In an analysis of suicide cases in Taiwan, doses of glyphosate/surfactant formulations in the range of 330±42 mL were associated with fatalities and the survivors were correlated with doses of 122±12 mL. Gastrointestinal effects (vomiting, abdominal pain, diarrhea), irritation, congestion, or other forms of damage to the respiratory tract, pulmonary edema, decreased urinary output sometimes accompanied by acute renal tubular necrosis, hypotension, metabolic acidosis, and electrolyte imbalances, probably secondary to the gastrointestinal and renal effects, are seen in human cases of glyphosate/surfactant exposure. It is speculated that the POEA surfactant component in the glyphosate formulations could be the dominant contributing factor leading to the effects seen in these suicide cases (USDA, 2003).

In terms of this risk assessment, however, only the increased use of glyphosate as an herbicide is being considered. According to EPA, glyphosate is considered to be of low acute toxicity by oral, dermal, and ocular routes of exposure, since all studies are in Toxicity Category III or IV, considered slightly to practically nontoxic, respectively. Furthermore, an acute inhalation study was waived by EPA because glyphosate is a nonvolatile solid and the studies conducted on the EUP formulation are considered sufficient (U.S. EPA, 2006, 1993). Additionally, according to the World Health Organization (WHO), glyphosate has been classified as unlikely to present an acute hazard in normal use (WHO, 1996). The EPA acute toxicity profile for glyphosate is presented in table L-4.

Table L-4. Acute Toxicity Profile of Glyphosate (U.S. EPA, 2006)

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

3.1.5 General Subchronic and Chronic Systemic Toxicology

One of the more consistent signs of subchronic or chronic exposure to glyphosate is reduced weight gain, which is consistent with experimental data indicating that glyphosate might be an uncoupler of oxidative phosphorylation. This effect has been noted in mice, rats, dogs, and rabbits. Additionally, the reduced weight gain observed was not associated with a significant decrease in food consumption. Other general and nonspecific signs of toxicity include liver weight, blood chemistry (could suggests mild liver toxicity), and liver pathology (USDA, 2003). The results of several subchronic and chronic toxicity studies are presented in table L-5 and discussed in the subsequent paragraphs.

Table L-5. Subchronic and Chronic Toxicity Profile of Glyphosate (U.S. EPA, 2006)

EPA Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity (Mouse)	NOAEL = 1500 mg/kg/day in males and females LOAEL = 4500 mg/kg/day in males and females based on reduced weight gain.
870.3100 90-Day oral toxicity (Range finding)	NOAEL = not established LOAEL = 50 mg/kg/day in males and females based on possible increased phosphorus and potassium values.
870.3150 90-Day oral toxicity (Rat) - AMPA - glyphosate metabolite	NOAEL = 400 mg/kg/day in males and females LOAEL = 1200 mg/kg/day in males and females based on body weight loss and histopathological lesions of the urinary bladder.

Table L-5. Subchronic and Chronic Toxicity Profile of Glyphosate (U.S. EPA, 2006)

EPA Guideline No./ Study Type	Results
870.3200 21/28-Day dermal toxicity (Rabbit)	NOAEL = 1000 mg/kg/day in males and females LOAEL = 5000 mg/kg/day based on slight erythema and edema on intact and abraded skin of both sexes, and decreased food consumption in females.
870.3485 28-Day inhalation toxicity (rat)	NOAEL = 0.36 mg/L (highest dose tested; HDT) LOAEL = not established based on 6 hours/day, 5 days/week for 4 weeks
870.4100b Chronic toxicity (dog)	NOAEL = 500 mg/kg/day in males and females (HDT) LOAEL = not established.

One of the studies included in table L-5 is a 90-day oral toxicity study in rats exposed to AMPA. As noted in the table and previously discussed, AMPA is a metabolite of glyphosate, and in soil and environmental water samples it is found more regularly than glyphosate. AMPA is considered slightly more toxic than glyphosate. However, while AMPA is a common environmental metabolite, only trace amounts of it are formed in mammals, with the remainder being excreted unchanged. For this reason, direct exposures to AMPA, as an endogenous metabolite in animals, are encompassed by the existing toxicity data on glyphosate. For further discussion on the occurrence of environmental concentrations of glyphosate or its metabolite AMPA, see the technical report: *Potential Impacts on Wildlife, Amphibians, Plants, and Ecosystems from Increased Glyphosate and Other Chemical Use* (appendix N).

Other studies conducted at the time of the 1993 reregistration of glyphosate include two subchronic feeding studies in rodents that showed effects in the blood and pancreas. In the first 90-day feeding study, Sprague-Dawley rats were fed glyphosate for three months in doses equivalent to 0, 63, 317, or 1,267 mg/kg/day for males and 0, 84, 404, or 1,623 mg/kg/day for females. Males and females in all treated groups showed increased serum phosphorus and potassium. The mid-dose group had increased serum glucose. Likewise, the high-dose had increased serum glucose, blood urea nitrogen, and serum alkaline phosphatase and an increased occurrence of pancreatic lesions. EPA determined that based on these results, the no observed effect level (NOEL) is <63 mg/kg/day for males and <84 mg/kg/day for females. However, these results were considered only possibly treatment related and the NOEL dose for each sex was not determined definitively (U.S. EPA, 1993).

In the second subchronic feeding study, CD-1 mice were fed diets containing 0, 250, 500 or 2,500 mg/kg/day of glyphosate for 90 days. The risk assessment parameters were set based on decreases of body weight gains in the high-dose males and females of about 24 percent and 18 percent, respectively. Based on the observed decrease in body weight gain, the NOEL for both sexes is 500 mg/kg/day and the lowest observed effect level (LOEL) is 2,500 mg/kg/day (U.S. EPA, 1993).

3.1.6 Effects on Nervous System

There was no evidence of neurotoxicity in any of the toxicology studies conducted and there are no data requirements for neurotoxicity studies. Moreover, analysis of detailed literature on health outcomes of accidental and intentional gross over-exposures, such as suicides, to glyphosate or its commercial formulations also do not implicate it in neurotoxicity effects. The weight of evidence suggests that any neurological symptoms associated with glyphosate exposures were secondary to other toxic effects and cannot be attributed to exposures directly (USDA, 2003). Based on weight of evidence considerations, EPA determined that it is not necessary to conduct a developmental neurotoxicity study with glyphosate to evaluate the potential for developmental neurotoxic effects (U.S. EPA 1993, 2006; USDA, 2003).

Some of the relevant studies are discussed in the following paragraphs. Many of the other neurological studies conducted presented results that were not considered scientifically robust and, therefore, are not discussed in further detail in this section (USDA, 2003).

Glyphosate has been tested for neurotoxicity in rats after both acute and subchronic exposures, and has been tested for delayed neurotoxicity in hens (USDA, 2003). In an acute study, 10 male and 10 female rats were given doses of 50, 100, or 200 mg of glyphosate a.e./kg and were observed for 2 weeks. In a subchronic study, 12 female and 12 male rats were exposed to glyphosate in their diet at concentrations of 2,000, 8,000, or 20,000 ppm for 13 weeks. In both studies, glyphosate was negative for signs of neurotoxicity. In a third study, 20 hens were given a single gavage dose of 2,000 mg/kg of glyphosate; a slight decrease in brain AchE activity occurred, but there were no signs of delayed motor ataxia or neuropathology (USDA, 2003).

An additional subchronic study in rats and mice, preformed by the National Toxicology Program (NTP, 1992), suggests that glyphosate could produce histological changes in the salivary glands in both organisms. While glyphosate can produce changes of the salivary gland by acting through an adrenergic pathway or by producing an adrenergic-mediated stimulation through some indirect mechanism, the mechanism causing this effect is not clearly understood and no signs of neurotoxicity were noted (USDA, 2003).

In an investigation of the effects of glyphosate on sensory mechanisms, a 1 mM or 10 mM dose of glyphosate was applied to the tongue of anesthetized gerbils. As a result, their taste tester response (to table salt, sugar, and acids) decreased. Due to the possibility of outside variables affecting experimentation, these results were not classified clearly as a glyphosate-induced neurological effect (USDA, 2003).

3.1.7 Effects on Immune System

Glyphosate has been tested for effects on the immune system in humans and experimental animals, in both *in vivo* and *in vitro* studies. In an *in vivo* study performed by Blakley (1997), mice were exposed to glyphosate in their drinking water, at concentrations of 0, 0.35, 0.70, or 1.05 percent, for 26 days; their antibody immune response was evaluated using sheep red blood cell challenge. The study found that the response in exposed mice did not differ from that of the unexposed mice (controls). Additionally, an *in vitro* study using human immunocompetent cells also indicated that glyphosate at concentrations ranging from 0.01 to 10 µmoles had no effect on

the immune system (Flaherty et al., 1991). Furthermore, there is also no evidence to suggest that glyphosate causes dermal sensitization or morphologic abnormalities, in experimental animals, which could implicate an effect on the immune system (USDA, 2003).

In studies performed on humans, there has been no confirmation that glyphosate directly causes photoirritation, photosensitization, or allergic responses (Williams et al, 2000; Jauhiainen et al., 1991; Maibach, 1986). In a 1986 study by Maibach, a group of volunteers were exposed to original Roundup® formulation via direct dermal application and no significant responses were observed.

3.1.8 Effects of Endocrine Function

Of the specific tests conducted to determine potential effects of glyphosate on the endocrine system, none have reported any potential estrogen, androgen, and/or thyroid mediated toxicity resulting from exposure to glyphosate (U.S. EPA, 2006; USDA, 2003).

Glyphosate was inactive as an estrogen receptor agonist in MCF-7 human breast cancer cells (Lin and Garry, 2000) and in yeast and trout hepatocyte assays (Petit et al., 1997). Additionally, in another study, the steroidogenic acute regulatory (StAR) protein, which mediates the rate-limiting step in the mitochondrial synthesis of steroid hormones, was not disrupted by glyphosate; therefore, glyphosate did not inhibit steroid synthesis in MA-10 mouse Leydig tumor cells. In a third test, glyphosate, with surfactant, was found to inhibit steroid synthesis. For all of these studies, it should be noted that they were conducted *in vitro*, and were used to assess whether a plausible biological mechanism for glyphosate to act as an endocrine disruptor exists (USDA, 2003). In 2009 EPA issued the first test orders for pesticide and other chemicals, including glyphosate, to be screened for their potential effects on endocrine system (Federal Register: October 21, 2009, Volume 74, Number 202). EPA notes that because this list was selected on the basis of their exposure potential only, it should not be construed or characterized of known or likely endocrine disruptors.

3.1.9 Reproductive and Teratogenic Effects

Exposure to glyphosate has been evaluated for its effects on reproduction and ability to cause birth defects (teratogenic effects). Most of the literature indicates that glyphosate does not directly cause reproductive or teratogenic effects (U.S. EPA, 2006, 1993; USDA, 2003). Four studies on the maternal, reproductive, and developmental toxicity of glyphosate were submitted for reregistration of glyphosate in 1993 (U.S. EPA, 2006, 1993). The results of the studies are presented in table L-6 and are discussed in the paragraphs that follow.

Table L-6. Reproductive and Teratogenic Toxicity Profile for Glyphosate (U.S. EPA, 2006)

Study Type	Results
870.3700a Prenatal developmental in rodents (Rat)	**Maternal** NOAEL = 1,000 mg/kg/day LOAEL = 3,500 mg/kg/day based on inactivity, mortality, stomach hemorrhages and reduced body weight gain. **Developmental** NOAEL = 1,000 mg/kg/day LOAEL = 3,500 mg/kg/day based on increased incidence in the number of fetuses and litters with unossified sternebrae and decreased fetal body weight.
870.3700b Prenatal developmental in (Rabbit)	**Maternal** NOAEL = 175 mg/kg/day LOAEL = 350 mg/kg/day based on mortality, diarrhea, soft stools, and nasal discharge. **Developmental** NOAEL = 350 mg/kg/day (HDT) LOAEL = not established.
870.3800 Reproduction and fertility effects, 3-generation (Rat)	**Parental/Systemic** NOAEL = 30 mg/kg/day (HDT) **Reproductive** NOAEL = 30 mg/kg/day (HDT) **Offspring** NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on focal dilation of the kidney in male F_{3b} pups.
870.3800 Reproduction and fertility effects, 2-generation (Rat)	**Parental/Systemic** NOAEL = 500 mg/kg/day in males and females LOAEL = 1,500 mg/kg/day in males and females based on soft stools, decreased body weight gain and food consumption. Focal dilation of the kidney observed at 30 mg/kg/day in the 3-generation study was not observed at any dose level in this study. **Reproductive** NOAEL ≥ 1,500 mg/kg/day (HDT) in males and females **Offspring** NOAEL = 500 mg/kg/day in males and females LOAEL = 1,500 mg/kg/day in males and females based on decreased body weight gain during lactation.

In the first study, Charles River COBS CD rats were dosed with 0, 300, 1,000, or 3,500 mg/kg/day of glyphosate by gavage during gestation days six through 19. The high dose dams showed signs of diarrhea; decreased mean body weight; breathing rattles; inactivity; red matter around the nose, mouth, forelimbs, and dorsal head; decreases in total implantations per dam and fetuses per dam; and mortality. Developmental effects were also only seen in the high-dose group and included increased numbers of litters and fetuses with unossified sternebrae and decreased mean fetal body weights. Based on these results, the maternal and developmental toxicity no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) are 1,000 mg/kg/day and 3,500 mg/kg/day, respectively (U.S. EPA, 2006, 1993; USDA, 2003).

In a second developmental and maternal toxicity study, Dutch Belted rabbits administered 0, 75, 175, or 350 mg/kg/day during gestation days six through 27 showed treatment-related findings at the highest dose only. These effects included diarrhea, nasal discharge, and death. There were no developmental effects observed, which could be attributable to the high maternal mortality level (62.5 percent at the highest dose). The NOAEL and LOAEL for maternal toxicity are 175 mg/kg/day and 350 mg/kg/day, respectively (U.S. EPA, 2006, 1993; USDA, 2003).

In a three-generation reproduction study on male and female Sprague-Dawley rats administered 0, 3, 10, or 30 mg/kg/day of glyphosate continuously through diet, increased incidence of focal tubular dilation of the kidney was seen in the high-dose male third generation pups. The recommended NOEL for reproductive toxicity is ≥30 mg/kg/day. The recommended

developmental toxicity NOAEL and LOAEL are 10 mg/kg/day and 30 mg/kg/day, respectively (U.S. EPA, 2006, 1993; USDA, 2003).

A two-generation reproduction study showed treatment-related effects at the high dose when Sprague-Dawley rats were administered 0, 100, 500, or 1,500 mg/kg/day of glyphosate continuously through the diet. These effects included soft stools in the F_0 and F_1 generations, decreased food consumption and body weight gain in the F_0 and F_1 generations during the growth period, and decreased body weight gain in the F_1 and F_2 generations during the second and third week of lactation. Based on these effects, both the systemic and developmental NOELs are 500 mg/kg/day and the systemic and development LOELs are 1,500 mg/kg/day (U.S. EPA, 2006, 1993).

Additional studies conducted to evaluate the reproductive and teratogenic effects of glyphosate, include subchronic and chronic exposure studies, which attempted to examine the impacts of glyphosate exposure on morphology of reproductive organs, mammary glands, and endocrine glands (including the testis, ovary, pituitary, thyroid, adrenal, pancreas, parathyroid, and thymus). In both subchronic and chronic studies, no treatment-related effects on reproductive organs or endocrine glands were observed at or below the maximally tolerated dose of 20,000 ppm in the diet in the chronic study (Stout and Ruecker, 1990) and 50,000 ppm in the subchronic study (NTP, 1992).

Furthermore, according to USDA (2003), two studies, by Yousef et al. (1996) and Schroeder and Hogan (1981), show conflicting results of glyphosate's effect on mating, fertility, and reproduction parameters (including libido level, ejaculate volume, sperm count, semen fructose level and osmolarity, and number of abnormal or dead sperm). Yousef et al. (1996) found that all of the effects seen in rabbits were statistically significant; however the study does not provide the actual doses used or specify the exact formulation. The study by Schroeder and Hogan (1981) suggests no treatment-related effects of glyphosate at doses of 3, 10, or 20 mg/kg bw, although some changes in kidney morphology were observed at 30 mg/kg/day. The basis for inconsistency lies in the reporting and experimental design limitations and deficiencies in Yousef's study. Also, the use of gelatin capsules in Yousef et al. (1996) makes the study less comparable and relevant to potential human exposure (USDA, 2003).

In terms of effects in humans, several epidemiological studies have been conducted to assess the relationship between general, or overall, pesticide exposure, or assumed pesticide exposure, and reproductive health outcomes; however, most of them have not characterized exposures to specific pesticides (Arbuckle and Sever, 1998). Of the few studies that have linked exposure to glyphosate to potential risks, no adverse reproductive effects were noted. For example, the Ontario Farm Health Study, three retrospective cohort studies (Arbuckle et al., 2001; Curtis et al., 1999; Savitz et al., 1997) collected data on the relationship between pregnancy outcomes and pesticide use among couples living on farms in Ontario. Risk of miscarriage, spontaneous abortions, and fecundity were all found to be unrelated to glyphosate formulation use and exposure (USDA, 2003).

3.1.10 Carcinogenicity and Mutagenicity

EPA (1993, 2002) and WHO (WHO, 1994, 2004) have reviewed, in detail, information regarding the carcinogenicity and mutagenicity of glyphosate. In 1991, EPA classified glyphosate as a Group E carcinogen (evidence of noncarcinogenicity for humans). Likewise, based on three studies submitted (and discussed in the following paragraphs) for the reregistration of glyphosate in 1993, EPA concluded that glyphosate is not carcinogenic at the levels tested (U.S. EPA, 2006, 1993). EPA confirmed this decision again in their publication of tolerance for glyphosate in 2002 (U.S. EPA, 2002).

In the first study considered during the reregistration of glyphosate in 1993, Sprague-Dawley rats were fed glyphosate at levels of 0, 3, 10, or 31 mg/kg/day in males and 0, 3, 11, or 34 mg/kg/day in females for 26 months. The high dose groups showed signs of increased incidence of thyroid C-cell carcinomas in females and interstitial cell testicular tumors, but the EPA determined that these neoplasms were not treatment-related, noted that the incidence of thyroid carcinomas was not statistically significant, and determined that the incidence of testicular tumors was within historical levels. Therefore, EPA determined that glyphosate was not considered carcinogenic in this study (U.S. EPA, 1993).

A second carcinogenicity feeding study was also conducted using Sprague-Dawley rats fed diets containing 0, 89, 362, or 940 mg/kg/day in males and 0, 113, 456, or 1183 mg/kg/day in females of glyphosate. The low- and high-dose males and females showed an increase incidence of pancreatic islet cell adenomas and hepatocellular (liver) adenomas. The mid- and high-dose animals also showed an increased incidence of thyroid C-cell adenomas. However, the pancreatic islet cell adenomas were not associated with a statistically significant positive dose-related trend, a progression to carcinomas, or dose-related increase in pancreatic hyperplasia. Additionally, a statistically significant increase in incidence of hepatocellular adenomas was not seen. The incidence was within historical range, there was no progression to carcinomas, and the incidence of hyperplasia was not compound-related. In terms of thyroid C-cell adenomas, there was no statistically significant dose-related trend in occurrence or a statistically significant increase in incidence, no progression to carcinomas, and no significant dose-related increase in hyperplasia. Therefore, glyphosate was not considered to be carcinogenic (U.S. EPA, 1993)

Another carcinogenicity study involved an 18-month feeding study conducted with CD-1 mice using doses of glyphosate equivalent to 0, 150, 750, or 4500 mg/kg/day. The effects in the high-dose group included decreased body weight gain in both sexes, increased hepatocellular hypertrophy, hepatocellular necrosis and interstitial nephritis in males, increased incidence of proximal tubule epithelial basophilia and hypertrophy in females, and an increased incidence of renal tubular adenomas in males. Based on the effects listed above, the NOAEL is 750 mg/kg/day for both sexes and the LOAEL is 4500 mg/kg/day for both sexes. However, it was determined by EPA and confirmed by other experts that the adenomas occurred spontaneously and that glyphosate is not considered carcinogenic based on the results of this study (U.S. EPA, 2006, 1993).

In the EPA (2002) assessment, EPA addressed concerns about studies performed by Hardell and Eriksson (1999a,b) which found that individuals in Sweden with a history of glyphosate exposure had an increased risk of developing non-Hodgkin lymphoma. A second study by

Hardell and Eriksson (1999b) found this risk to be statistically significant. After careful review, EPA concluded that these studies do not provide a sufficient link to cancer and the results were based solely on unverified recollection of exposure to glyphosate-based herbicides; as a result, EPA maintained its classification of glyphosate as a Group E carcinogen. A more recent study by De Roos et al. (2005) concluded that there is no association between glyphosate exposure and "all cancer" incidence or most of the specific cancer subtypes they evaluated, including non-Hodgkins lymphoma. In a study by Eriksson et al. (2008), exposures were assessed by questionnaires with information supplemented over the phone, which raises classical recall bias complicated further by interviewer bias, which were not addressed in paper. A study by Bolognesi et al. (2009) used improved exposure assessment using cytogenic biomonitoring and concluded that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for eradication of coca and poppy is of low biological relevance. These studies would appear to continue support for a conclusion that glyphosate is not likely to be carcinogenic in humans.

In terms of its mutagenicity, glyphosate has been shown to cause an increase in chromosomal aberration in a plant (*Allium sp.*) associated with cell abnormalities in spindle fiber (Rank et al., 1993), DNA adduct formation in mice (Reluso et al., 1998), and single strand DNA breaks in mice (Bolognesi et al., 1997). Reports on *in vitro* studies conducted by Vyse and Vigfusson (1979) and Vigfusson and Vyse (1980) indicate a significant increase in sister chromatid exchanges in human lymphocytes and conclude that glyphosate is a slight mutagen. Another positive assay was confirmed in a fruit fly study (Kaya et al., 2000; Kale et al., 1995) as well as in a study of lymphocyte cultures (Lioi et al., 1998a; Lioi et al., 1998b). Most of the remaining screening studies for mutagenicity, however, were negative.

For example, four mutagenicity studies were submitted for the reregistration of glyphosate in 1993. These studies included a gene mutation assay in an Ames Test on *Salmonella typhimurium* strains, a gene mutation assay in Chinese hamster ovary cells/hypoxanthine – guanine – phosphoribosyl transferase assay, a Structural Chromosomal Aberration Assay in male and female Sprague-Dawley rats, and a combined study employing a rec-assay using *B. subtilis* a reverse mutation assay using *E. coli* and *Salmonella typhimurium* strains. None of these studies showed a mutagenic or clastogenic response. As a result, EPA concluded that glyphosate is not a mutagen (USDA, 2003; U.S. EPA, 2002, 1993).

3.1.11 Irritation and Sensitization

According to EPA, glyphosate is classified as mildly irritating to the eyes (Category III) and slightly irritating to the skin (Category IV) based on data collected from skin and eye irritation studies during the registration process (U.S. EPA 2006, 1993). Different formulations of glyphosate have different irritation patterns (e.g., the free acid of glyphosate is severely irritating to the eyes, but the IPA salt of the glyphosate is nonirritating to the skin and eyes) (USDA, 2003). Additionally, skin sensitization tests for glyphosate were all negative (U.S. EPA, 2006, 1993).

3.1.12 Systemic Toxic Effects from Dermal Exposure

Systemic toxic effects from chronic dermal exposure are less damaging than those from chronic oral exposure because glyphosate is poorly absorbed from the skin. Acute dermal exposure effects are similar to those of acute oral exposure effects (USDA, 2003). EPA classified glyphosate as a Category III for oral and dermal toxicity. The LD_{50} value for the acute oral toxicity of glyphosate is >5,000 mg/kg (U.S. EPA, 2006).

The EPA RED for glyphosate (U.S. EPA, 1993) gives more insight on the dermal toxicity of glyphosate. It cites a 1982 study (MRID 00098460) with rabbits in which glyphosate was applied to intact and abraded skin at doses of 10, 1,000, or 5,000 mg/kg/day, five days a week, for three weeks. The effects were minimal and included, slight irritation of the abraded skin and decreased food consumption, and decreased serum lactic dehydrogenase activity at 5,000 mg/kg. In a more recent study by Pinto (1996), dermal doses of 250, 500, or 1,000 mg/kg/day caused no effects on body weight, food consumption, hematology, clinical chemistry, or organ weights. There were also no signs of irritation or pathologic changes in tissue.

3.1.13 Inhalation Effects

EPA did not require an acute inhalation study for technical grade glyphosate (U.S. EPA, 2006, 1993) because of its low volatility rate. The acute inhalation LC_{50} value of the isopropylamine salt glyphosate is >6.37 mg/L, which is equivalent to a finding of no mortality in any of the five rats of each sex exposed to this concentration for four hours (USDA, 2003). A study conducted by Jamison et al., (1986) exposed a group of human volunteers to glyphosate treated flax dust and untreated flax dust. The glyphosate treated dust consistently caused a decrease in respiratory function; however, this might have been due to a greater distribution of smaller dust particles, which are more easily inhaled, in the glyphosate treated dust.

3.1.14 Toxic Relevance of Surfactants in Glyphosate Formulations

Various formulations of glyphosate contain POEA at a level of up to approximately 20 percent (200 g/L). Tallow contains a variety of fatty acids (e.g., oleic, palmitic, stearic, myristic, and linoleic acids), as well as smaller amounts of cholesterol, arachidonic, elaidic, and vaccenic acids. While surfactants are typically classified as “inert” components in herbicides with regard to pesticide action, they are not toxicologically inert and in many cases they are found to be more toxic than the herbicide itself (USDA, 2003).

A study evaluating the toxicity of the POEA surfactant includes a series of teratology tests in rats using glyphosate (98.7 percent purity), POEA used in glyphosate formulations, and the phosphate ester neutralized POEA. Groups of pregnant female rats were dosed with glyphosate at 300, 1,000, or 3,500 mg/kg/day; POEA at 15, 100, or 300 mg/kg/day, or the neutralized POEA at 15, 50, or 150 mg/kg/day on days 6 through 19 of gestation. Results indicated that severe maternal poisoning occurred at the 3,500 mg/mg/day dose of glyphosate, in association with reduced fetal body weight and sternal ossification, as well as fetal death. At a dose of 300 mg/kg/day of POEA and 150 mg/kg/day of neutralized POEA maternal deaths were also reported. Other noteworthy results in dams were signs of mild clinical toxicity and decreased food consumption that occurred at a dose of 100 mg/kg/day POEA surfactant. No fetotoxic

effects were reported at any dose level. Based on these results, the NOAELs for glyphosate, POEA, and neutralized POEA were 1000 mg/kg/day, 15 mg/kg/day, and 50 mg/kg/day, respectively (USDA, 2003).

There has been some debate as to the acute toxicity of POEA and the determination of its LD_{50} value, as compared to glyphosate; however, it is generally agreed that the acute toxicity of glyphosate formulations in humans (glyphosate and surfactant, LD_{50} in rats 5400 mg/kg/day) is almost equivalent to that of glyphosate (LD_{50} in rats 5600 mg/kg/day) (USDA, 2003). Additionally, based on drinking water studies on both glyphosate and Roundup® (glyphosate with POEA), the surfactant does not affect the rapid elimination rate of glyphosate in mammals (NTP, 1992).

3.1.15 Toxic Relevance of Impurities in Glyphosate Formulations

3.1.15.1 N-nitrosoglyphosate (NNG)

Technical grade glyphosate contains at least one impurity, N-nitrosoglyphosate (NNG). EPA determined that the NNG content in glyphosate was not toxicologically significant because more than 92 percent of the individual technical glyphosate samples tested contained less than 1.0 ppm NNG. There is general concern for the carcinogenic potential of nitroso compounds; however, it is hard to quantify (USDA, 2003; U.S. EPA, 1993).

3.1.15.2 4-Dioxane

1,4-Dioxane is an impurity in POEA, and EPA considers it to be a carcinogen (Class B2: Probable human carcinogen) and has derived a cancer potency factor (slope factor) of 0.011 mg/kg/day. 1,4-Dioxane is present in Roundup® at a level of approximately 0.03 percent or 300 mg/l (330 ppm). It has been demonstrated that dioxane does not present unique toxic effects; therefore, its toxicity (except its role as a carcinogen) is encompassed by the available toxicity data on glyphosate (USDA, 2003).

3.2 Exposure Assessment

3.2.1 Overview

As previously stated, there are five herbicide EUPs containing glyphosate that are recommended for use on a specific brand of GT alfalfa called Roundup Ready® alfalfa. These products include: Roundup Original Max®, Roundup Weather Max®, and Roundup Ultra Max II®, Honcho® and Honcho Plus® (Greenbook, 2008; Monsanto, 2008). Each of these products contains between 41 and 49 percent glyphosate (Monsanto, 2007a, 2007b, 2007c, 2007d, 2004). Independent consideration of other ingredients in the EUPs is beyond the scope of this exposure assessment. For purposes of this screening analysis, exposure estimates to the chemical glyphosate are presented as opposed to exposure estimates to the EUPs. This is because toxicological data on the EUPs, which are required to assess risk to workers, were not available at the time of the analysis.

3.2.2 Routes of Exposure

The general public is not at a high risk of exposure to substantial levels of glyphosate under typical conditions (U.S. EPA, 1993; USDA, 2003). Dermal and inhalation routes of exposure are not considered in this analysis because it is assumed that GT alfalfa will not be grown by members of the general public. Thus, it is assumed that the general public will not directly come in contact with or inhale herbicides recommended for use on GT alfalfa. It is, however, assumed that members of the general public could be exposed orally to these herbicides via consumption of foods that have been treated by herbicides containing glyphosate.

In the 1993 EPA RED for glyphosate, EPA conducted a dietary risk assessment and determined that non-nursing infants under one year of age are at highest risk of adverse effects associated with glyphosate exposure (U.S. EPA, 1993). EPA completed an additional risk assessment for glyphosate in 2006 to address its specific use on Indian mulberry and dried peas (U.S. EPA, 2006). In this later assessment, EPA also found that infants under one year of age are at greatest risk. The results of these risk assessments are discussed in further detail in section 3.4.

Because oral exposure scenarios are feasible, this exposure analysis estimates potential glyphosate exposure associated with consumption of fruit and vegetables that have been treated with an herbicide containing glyphosate. It is not anticipated that alfalfa will be consumed in large quantities directly by humans; alfalfa sprouts are consumed generally in relatively small quantities. Because small quantities of alfalfa sprouts are consumed, potential glyphosate consumption was estimated by modeling contamination of other crops growing nearby alfalfa fields.

Consumption of crops treated with a glyphosate-based herbicide is rare because treated crops show signs of damage, making the contamination easily identifiable to the consumer. However, it cannot be assumed that consumption will never occur, thus, exposure scenarios evaluated in this analysis include adults' chronic and acute consumption of contaminated fruit and vegetables. Exposures of two additional sensitive subpopulations including the elderly and infants less than one year of age are also estimated. Additional oral exposure scenarios might include consumption of contaminated water or fish, but analysis of these exposure pathways was not conducted for this assessment. Fish do not bioaccumulate glyphosate; in 2003, the USDA evaluated several water exposure scenarios, including consumption of contaminated surface water, and none were considered a risk to human health.

3.2.3 Application Rates

Maximum single application rates of products containing glyphosate for GT crops range from 0.56 pounds of glyphosate a.e. per acre up to 3.75 pounds of glyphosate a.e. per acre (Monsanto, date unknown). Application rates were determined using specific product labels for each EUP recommended for use on GT alfalfa (Monsanto, 2007a, 2007f, 2007c, 2007d, 2005b, 2005c, 2004). The maximum label single use rate for GT alfalfa is 1.55 pounds glyphosate a.e. per acre. Application rates on these products were presented in volume (i.e., quarts or ounces) of active ingredient per acre. These values were converted to mass (i.e., pounds) per acre by multiplying the application volume by the density of the EUP (See equations L-1 and L-2).

Equation L-1

Density = Mass / Volume

thus,

Equation L-2

*Mass = Density * Volume*

Density values were provided by material safety data sheets for each EUP. When product density was not available, the specific gravity of the EUP was used to calculate density. The specific gravity is the ratio of the product density to the density of water. It was assumed that the density of water is 1000 kg/m^3 (See equations L-3 and L-4).

Equation L-3

Specific gravity = Product density / Water density

thus,

Equation L-4

*Product density = Specific gravity * Water density*

Labels also provided application rates for the EUP as opposed to the chemical alone. Because this exposure analysis focuses on the chemical as opposed to the EUP, the percent a.e. (i.e., glyphosate) reported by the product label was considered in the exposure equation (See equation L-5). The percent of glyphosate in EUPs ranged from 41 and 49 percent (see table L-1).

Equation L-5

*Application rate of glyphosate = Application rate of EUP * Percent glyphosate in EUP*

Maximum application rates of the five EUP recommended for use on GT alfalfa are presented in table L-7. Please refer to appendix L-4 of this technical report for further explanation of application rate calculations.

Table L-7. Maximum Application Rates of EUPs for Use on Glyphosate-Tolerant Alfalfa

Product	Single Use Application Rate	Reference
Honcho®	2.0 lb a.i./acre	Monsanto, 2007a; 2007e
Honcho Plus®	2.0 lb a.i./acre	Monsanto, 2007b; 2007f
Roundup Original MAX®	1.9 lb a.i./acre	Monsanto, 2007c
Roundup WeatherMAX®	1.9 lb a.i./acre	Monsanto, 2007d; 2005a; 2005b
Roundup Ultra MAX II®	1.9 lb a.i./acre	Monsanto 2005c; 2004; 2003

3.2.4 General Public Exposure Scenarios

3.2.4.1 Acute Consumption Scenario

Exposure scenarios for acute consumption were provided by USDA (2003) and acute exposure algorithms were provided by SERA (2006) in a supplemental calculations worksheet presented to USDA. In this scenario, an individual is exposed through consumption of contaminated vegetables or fruit after a single acute spray application of glyphosate. An acute oral dose (OD_{acute}) of glyphosate can be estimated by multiplying the concentration of the chemical present on the contaminated vegetables or fruit (*Conc*) by the amount of that vegetables or fruit consumed per day per unit body weight of the exposed individual (*Amnt*) (See Equation L-6). The estimate of the concentration of the chemical present on the contaminated vegetables or fruit (*Conc*) is calculated by multiplying the application rate (*AR*), the residue rate (*RR*), the drift proportion (*Drift*), and the proportion of chemical remaining after washing (*Prop*) (See equation L-7).

Equation L-6

$$OD_{acute} = Conc * Amnt$$

Where:

OD_{acute}	=	estimated acute oral dose (mg/kg bw)
Conc	=	concentration on vegetation (mg/kg food item)
Amnt	=	amount consumed per day per unit body weight (kg food/kg bw/day)

Equation L-7

$$Conc = AR * RR * Drift * Prop$$

Where:

Conc	=	concentration on vegetation (mg/kg food item)
AR	=	application rate (lbs/acre)
RR	=	residue rates (mg/kg food per lb/acre)
Drift	=	drift proportion (unitless)
Prop	=	proportion remaining after washing (unitless)

The amounts of fruit or vegetables consumed by individuals (*Amnt*) are based on the estimates from the EPA *Exposure Factor's Handbook* (U.S. EPA, 1997). Data are based on an EPA analysis of the USDA (1991) nationwide survey called the Consumption of Food Intake by Individuals (CSFII) from 1989 to 1991. Data are in kilograms of fruit or vegetables consumed per kilogram of body weight of the individual per day (U.S. EPA, 1997). Data are already normalized to the body weights of the exposed individuals. Amounts of fruits and vegetables consumed by adults aged 20 to 39 years, elderly individuals aged 70 years and older, and infants under one year were collected. For each age category, the mean consumption rate is presented as the central estimate of consumption. Also for each age category, the 25th percentile of the distribution of consumption rates for the entire population of the age category evaluated in the CSFII is presented as the lower estimate, and the 100th percentile of the distribution is presented as the upper estimate of consumption. Consumption rates for fruits and vegetables by age category are presented in table L-8 and table L-9, respectively.

Table L-8. Amount of Fruit Consumed by Age Category (in kg of fruit per kg of body weight per day) (U.S. EPA, 1997)

Age Group	Mean (Central Estimate)	25th Percentile (Lower Estimate)	100th Percentile (Upper Estimate)
Adult (20-39 yrs)	1.88E-03	0	4.16E-02
Elderly (70+ yrs)	2.98E-03	8.90E-04	1.50E-02
Infants (<1 yr)	1.49E-02	0	2.11E-01

Table L-9. Amount of Vegetables Consumed by Age Category (in kg of vegetables per kg of body weight per day) (U.S. EPA, 1997)

Age Group	Mean (Central Estimate)	25th Percentile (Lower Estimate)	100th Percentile (Upper Estimate)
Adult (20-39 yrs)	3.53E-03	2.06E-03	1.71E-02
Elderly (70+ yrs)	4.07E-03	2.47E-03	1.89E-02
Infants (<1 yr)	6.80E-03	0	4.50E-02

An application rate (*AR*) of 2.0 pounds a.i. per acre was used because it is the more conservative of the single use application rates for the five EUPs recommended for use on GT alfalfa (See table L-7). This rate is consistent with the labeled maximum single use rate of 1.55 a.e. pounds glyphosate per acre for application on GT alfalfa.

Residue rates (*RR*) were based on an empirical relationship between application rate and concentration on food developed by Fletcher et al. (1994). Fletcher et al. used the Kenaga nomogram, a device developed by EPA to predict maximum potential pesticide residue levels. Fletcher et al. conducted a review to determine if the residue levels predicted by the nomogram are comparable to values reported in the literature. The authors concluded that the Kenaga nomogram predicts values for residue rates that are comparable to values reported in the literature. According to Fletcher et al., the estimated values range from 7 mg/kg food per lb/acre to 15 mg/kg food per lb/acre for fruit and from 45 mg/kg food per lb/acre to 135 mg/kg food per lb/acre for vegetation.

It was assumed that both the drift proportion (*Drift*) and the proportion of chemical remaining on the fruit or vegetation after washing (*Prop*) are equal to one. The drift proportion or spray drift of a pesticide is defined by EPA as the physical movement of a pesticide or herbicide through the air at the time of application to a site that is not intended for application (U.S. EPA, 2008). A drift proportion of one assumes that the same amount of pesticide is applied to target and nontarget crops. In this case, the herbicide target is GT alfalfa. It is unlikely that nontarget fruit or vegetation would have the same level of contamination as the target plant since they are likely to grow in different fields. Thus, a drift proportion of one is a highly conservative estimate. The proportion of the chemical remaining on the fruit or vegetation is likely to be reduced after washing, thus one is also a highly conservative estimate.

Central, lower, and upper bound exposure estimates from ingestion of fruit and vegetables were calculated for the acute oral consumption exposure scenarios for adults, the elderly, and infants. Results are presented in tables L-10 and L-11. Please refer to the calculations worksheet submitted with this report for further explanation of exposure estimate calculations.

Table L-10. Screening Exposure Estimates for Acute Consumption of Fruit by Age Category (in mg/kg bw/day)

Age Category	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Adult (20-39 yrs)	2.63E-02	0	1.25E+00	1
Elderly (70+ yrs)	4.17E-02	1.25E-02	4.50E-01	2
Infants (<1 yr)	2.09E-01	0	6.32E+00	3

Table L-11. Screening Exposure Estimates for Acute Consumption of Vegetables by Age Category (in mg/kg bw/day)

Age Category	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Adult (20-39 yrs)	3.18E-01	1.85E-01	4.61E+00	4
Elderly (70+ yrs)	3.66E-01	2.22E-01	5.11E+00	5
Infants (<1 yr)	6.12E-01	0	1.21E+01	6

3.2.4.2 Chronic Consumption Scenario

Exposure scenarios for chronic consumption scenario were provided by USDA (2003) and chronic exposure algorithms were provided by SERA (2006) in a supplemental calculations worksheet presented to USDA. In this scenario, the contaminated fruit or vegetation is exposed to glyphosate for a defined period of exposure (*ED*). The general public's consumed dose of glyphosate ($OD_{chronic}$) can be estimated by multiplying the time-weighted average concentration of consumed vegetation ($C_{TWA\ CON}$) by the amount of vegetation or fruit consumed per day per unit body weight (See equation L-8). The $C_{TWA\ CON}$ is calculated by multiplying the time-weighted average concentration on food over the exposure duration (Con_{TWA}) by the proportion of the chemical remaining after the food item is washed (*Prop*) (See equation L-9). The time-weighted average concentration on food over the exposure duration (Con_{TWA}) is estimated in equation L-10 (De Sapio, 1976). The concentration at a specific time ($Conc_{ED}$) can be calculated based on the initial concentration on food (C_0), assuming a first-order decrease in concentrations in contaminated food (See equation L-11). C_0 is estimated by multiplying the application rate by the residue rate (*RR*) and the proportion of anticipated spray drift (See equation L-12). The decay coefficient (*k*) is estimated by dividing the natural log of 2 (*Ln(2)*) by the half-life of the chemical on the food item (t_{50}) (See equation L-13).

Equation L-8

$$OD_{chronic} = C_{TWA\ CON} * Amnt$$

Where:

$OD_{chronic}$	=	estimated chronic oral dose (mg/kg bw)
$C_{TWA\ CON}$	=	time-weighted average concentration on consumed food item over exposure duration (mg/kg)
Amnt	=	amount consumed per day per kilogram of body weight (kg food item/kg bw/day)

Equation L-9

$$C_{TWA\ CON} = Con_{TWA} * Prop$$

Where:

$C_{TWA\ CON}$	=	time-weighted average concentration on consumed food item over exposure duration (mg/kg food)
Con_{TWA}	=	time-weighted average concentration on food over exposure duration (mg/kg food)
Prop	=	proportion remaining after food item is washed (unitless)

Equation L-10

$$Con_{TWA} = C_0 \times (1-e^{-k*ED}) \div (k * ED)$$

Where:

Con_{TWA}	=	time-weighted average concentration on food over exposure duration (mg/kg food)
C_0	=	initial concentration on vegetation (mg/kg food)
k	=	decay coefficient (per day)
ED	=	time (days)

Equation L-11

$$Conc_{ED} = C_0 * e^{-k*ED}$$

Where:

$Conc_{ED}$	=	concentration on food at a specific time (mg/kg food)
C_0	=	initial concentration on vegetation (mg/kg food)
k	=	decay coefficient (per day)
ED	=	time (days)

Equation L-12

$$C_0 = AR * Drift * RR$$

Where:

C_0	=	initial concentration on food item (mg/kg food)
AR	=	application rate (lbs/acre)
Drift	=	spray drift (unitless)
RR	=	residue rate (mg/kg food/lb/acre)

Equation L-13

$$k = Ln(2) / t_{50}$$

Where:

k	=	decay coefficient (per day)
Ln(2)	=	natural log of 2 (unitless)
t_{50}	=	dissipation half-life of residues on foods (days)

For the chronic oral exposure scenarios, a number of variables are comparable to variables incorporated in the equations used to estimate acute exposure. Values for the amount of fruit and vegetables consumed (*Amnt*) are the same as the values used for the acute oral exposure scenarios. Consumption rates for each age category (adults aged 20-39 years, elderly individuals aged 70+ years, and infants under 1 year) were taken from the EPA *Exposure Factors Handbook* (U.S. EPA, 1997). The proportion of the chemical remaining after a food item is washed (*Prop*) is also assumed to be one. The same application rate (*AR*) of 2 pounds of glyphosate a.i per acre was also used and the same residue rates (*RR*) for fruits and vegetables from Fletcher et al. (1994) were assumed for the chronic exposure scenario and the acute exposure scenario. The same spray drift (*Drift*) assumption of one was also assumed for the chronic scenario.

Several additional default values were required for the chronic exposure scenarios that were not required for the acute exposure scenario. An exposure duration (*ED*) of 90 days was assumed based on the USDA assumption that a harvesting season will last approximately three months (USDA, 2003). Thus, it is assumed that an individual could be exposed for 90 consecutive days during this season. Calculation of the decay coefficient (*k*) required a half life of the chemical on food. Siltanen et al. (1981) used the dissipation on the vegetation to estimate the half-life of glyphosate on fruits and vegetation. The study reported a half-life of 46 days which is the value assumed in this analysis.

Central, lower, and upper bound chronic exposure estimates from ingestion of fruits and vegetables were calculated for adults, the elderly, and infants. Results are presented in tables L-12 and L-13. Please refer to the calculations worksheet submitted with this report for further explanation of exposure estimate calculations.

Table L-12. Screening Exposure Estimates for Chronic Consumption of Fruit by Age Category (in mg/kg bw/day)

Age Category	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Adult (20-39 yrs)	1.44E-02	0	6.83E-01	7
Elderly (70+ yrs)	2.29E-02	6.82E-03	2.46E-01	8
Infants (<1 yr)	1.14E-01	0	3.46E+00	9

Table L-13. Screening Exposure Estimates for Chronic Consumption of Vegetables by Age Category (in mg/kg bw/day)

Age Category	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Adult (20-39 yrs)	1.74E-01	1.01E-01	2.52E+00	10
Elderly (70+ yrs)	2.00E-01	1.22E-01	2.80E+00	11
Infants (<1 yr)	3.35E-01	0	6.65E+00	12

3.3 Dose-response assessment

3.3.1 Overview

An RfD is defined as a level of exposure that will not result in any adverse effects in any individual. The RfD value for glyphosate proposed by the.EPA Office of Pesticide Programs is 2 mg/kg/day, and is based on a teratogenicity study in rabbits in which there were no observed effects in offspring at any dose level, and maternal toxicity was noted at 350 mg/kg/day with a NOAEL of 175 mg/kg/day (Rodwell et al., 1980b). The RfD of 2 mg/kg/day was derived by dividing the NOAEL by an uncertainty factor of 100 – 10 for sensitive individuals and 10 for species-to-species extrapolation – and rounding the result to one significant figure (U.S. EPA, 2006, 2002, 1993).

3.3.2 Existing Guidelines

The current section of this risk assessment attempts to take into account the two chronic RfDs that the EPA Office of Pesticide Programs (EPA OPP) proposed for glyphosate, and the WHO comparable proposed acceptable daily intake (ADI) in its analysis. As discussed in the previous paragraph, the RfD of 2 mg/kg/day was derived from a teratogenicity study in rabbits and was first derived in the 1993 RED document for glyphosate (U.S. EPA, 1993). EPA has also derived an RfD for glyphosate of 0.1 mg/kg/day (U.S. EPA, 1990). This RfD was originally derived by the EPA Integrated Risk Information System (IRIS) workgroup and is still posted on IRIS. This value is based on a dietary 3-generation reproduction study by Schroeder and Hogan (1981), in which rats were exposed to glyphosate in their diet and no adverse effects were observed. The NOAEL was 10 mg/kg/day and an uncertainty factor of 100 was used.

The ADI proposed by WHO (1994) is based on a life-time feeding study in rats, as opposed to a reproductive toxicity study. A study by Lankas and Hogan (1981) supplied male and female rats a daily dose (0, 3.1, 10.3, or 31.5 mg/kg/day in males; 0, 3.4, 11.3, or 34.0 mg/kg/day in females) of glyphosate in their diet for 26 months. No effects were observed in any of the animals at any of the dose levels; therefore, WHO used a NOAEL of 31.5 mg/kg/day and an uncertainty factor of 100 to derive the ADI.

The EPA Office of Drinking Water (EPA ODW) proposed a 10-day health advisory for glyphosate of 17.5 mg/L, based on the NOAEL of 175 mg/kg/day, and a longer-term health advisory of 1 mg/L, based on the EPA RfD of 0.1 mg/kg/day. EPA ODW also derived a short-term RfD of 2 mg/kg/day, which is identical to the chronic RfD proposed by EPA OPP.

3.3.3 Dose-Response and Dose-Severity Relationships

A threshold and nonthreshold multistage model was used to estimate the LD_{50} in humans. Both models approximated the LD_{50} to be 3,000 mg/kg/day, similar to the range of 2000 to 6000 mg/kg reported in experimental mammals. Additionally, the threshold version of the multistage model was also used to yield an estimate of the threshold dose of 445 mg/kg for systemic toxic effects. Below this dose, it is assumed that no individual in the population will respond (USDA, 2003).

In addition, dose severity relationships were analyzed for experimental mammals and humans. The available animal data were characterized using four standard severity levels: NOEL, NOAEL, adverse effect level and frank effect level. Furthermore, three different groups of end points were determined: general systemic toxic effects, reproductive or developmental effects, and acute LD_{50} values. Although the exposure periods for these studies ranged from one day to greater than two years, glyphosate is rapidly excreted from the body; therefore, duration of exposure is not an important parameter in assessing the toxicity of glyphosate (USDA, 2003).

The data for experimental animals were further analyzed using categorical regression analysis in the next step of assessing the dose-severity relationships, which correlates categorical responses with factors that might influence the response. Results of the categorical regression indicate that the probability of an adverse effect at the RfD of 0.1 mg/kg/day is 0.0005, at 1 mg/kg/day is 0.003, and at a dose of 10 mg/kg/day is 0.12. From these results, it was inferred that an RfD of 2 mg/kg is protective. It was further determined that the probability of a frank toxic effect (a sufficiently severe effect that can be observed in the whole organism without the use of invasive methods) at the RfD of 0.1 mg/kg/day is 0.00005 and at the RfD of 2 mg/kg/day increases to 0.0006 (USDA, 2003).

The consistency between the categorical analysis in experimental animals and the dose-response analysis using the multistage model for humans is relatively good. At 445 mg/kg, the estimated threshold of human lethality, the probability of observing a frank toxic effects is approximately 0.04. At this dose in the nonthreshold version of the multi-stage model, the probability is 0.02. At the estimated human LD_{50} of approximately 3000 mg/kg, the probability of observing an adverse or frank effect, as determined by a categorical regression using two categories, is 0.7.

For glyphosate, the data suggest that humans are no more sensitive than experimental animals. Subsequently, this suggests that the current and proposed RfDs could be overly protective by a factor of 10 or greater.

3.3.4 Susceptible Populations

On the basis of developmental studies in rats and rabbits and reproductive findings in rats, glyphosate exhibited no evidence of increased qualitative and quantitative susceptibility to offspring with pre-natal or post-natal exposures. Additionally, an acute RfD was not established for any population subgroup or the general population, including infants and children, based on the absence of an appropriate toxicological endpoint attributable to a single exposure (dose), including maternal toxicity in developmental toxicity studies (U.S. EPA, 2006).

3.3.5 RfD Values Used in Risk Assessment of Glyphosate

The database on glyphosate is large, complex, and open to many potential interpretations. For example, according to a 1986 determination by the Joint Food and Agricultural Organization of the United Nation /WHO on Pesticides Residues, an ADI of glyphosate is 0.3 mg/kg bw/day (WHO, 1986). This was based on a 26-month feeding study in rats with a resulting NOEL of >31 mg/kg/day and an uncertainty factor of 100. EPA determined a NOAEL of 175 mg/kg/day and an uncertainty factor of 100, because maternal mortality was observed at the highest dose group. As a result, in 1992, the EPA Office of Pesticide Program Reference Dose Peer Review

Committee recommended that the RfD for glyphosate be set at 2 mg/kg/day (USDA, 2006) for longer-term exposures. The EPA ODW also recommended a value of 2 mg/kg/day for short-term exposures. As a result, the same RfD is used for both short- and long-term exposures; however, due to a lack of significant dose-response data for glyphosate, this approach was deemed appropriate (USDA, 2006; U.S. EPA 2002, 1993). Glyphosate endpoints for this risk assessment are summarized in table L-14 below.

Table L-14. Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Health Risk Assessments (U.S. EPA, 2006)

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (all populations)	NOAEL= 175 mg/kg/day UF = 100 **Chronic RfD** = 1.75 mg/kg/day = 2.0 mg/kg/day (rounded to one significant figure)	FQPA SF = 1X **cPAD** = cRfD / FQPA SF = **1.75 mg/kg/day**	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, and Intermediate-Term Incidental, Oral (Residential)	NOAEL = 175 mg/kg/day	LOC for MOE = 100	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, Intermediate- and Long-Term Dermal (1 - 30 days, 1-6 months, 6 months – lifetime) (Occupational/Residential)	None	None	Based on the systemic NOAEL of 1,000 mg/kg/day in the 21 day dermal toxicity study in rabbits, and the lack of concern for developmental and reproductive effects, the quantification of dermal risks is not required.
Short-, Intermediate- and Long-Term Inhalation (1-30 days, 1- 6 months, 6 months-lifetime) (Occupational/Residential)	None	None	Based on the systemic toxicity NOAEL of 0.36 mg/L (HDT) in the 28-day inhalation toxicity study in rats, and the physical characteristics of the technical (wetcake), the quantification of inhalation risks is not required.
Cancer (oral, dermal, inhalation)	**Classification:** Group E; no evidence of carcinogenicity; risk assessment not required		

3.3.6 Other Chemicals

For the purpose this risk assessment, the discussion on "other chemical usage" will be limited to describing the herbicides that glyphosate will be replacing and will be qualitative in nature. In order to thoroughly assess glyphosate's toxicity as compared to "other chemicals" it would be necessary to do a complete risk assessment on each "other chemical."

Glyphosate is more environmentally and toxicologically benign than many of the herbicides that it replaces (Cerdeira and Duke, 2006). Peterson and Hulting (2004) compared the ecological risks of glyphosate used in GT wheat with 15 other herbicides used in spring wheat in the northern United States. Great Plains (MN, ND, SD, WY, and MT). The herbicides were as follows: 2,4-D, bromoxynil, clodinafop, clopyralid, dicambia, fenoxaprop, flucarbazone, 2-methyl-4-chlorophenoxyacetic acid (MCPA), metasulfuron, thifensulfuron, tralkoxydim, triallate, triasulfuron, tribenuron, and trifluralin. The ecological risks for the 15 herbicides relative to glyphosate were highly variable, with glyphosate having less relative risk to nontarget terrestrial and aquatic plant life and groundwater than most other active ingredients. The study predicted that glyphosate use in GT crops will be less toxic to terrestrial and aquatic wildlife than several of the herbicides which they replace (Peterson and Hulting, 2004).

The other major ecological concern from glyphosate use in GT crops is the development of glyphosate-resistant weeds. Weeds can develop resistance to herbicides for the following reasons: frequent exposure to a particular herbicide, the spread of naturally resistant weed seeds, and the outcrossing of herbicide-tolerant genes from genetically altered plants to weedy relatives. In the event of glyphosate-resistant weeds the management practices suggested are use the following less resistant-prone herbicides recommended for use: paraquat/diquat, MSMA, phenoxy herbicide (e.g., 2,4-D, MCPA, trichlopyr, dicamba), tubulin inhibitors (e.g., benefin, fluchloralin, pendimethalin, ethanlfluralin, trifluralin), triazine (amitrole, atrazine, cyanazine, simazine, trietazine, metribuzin) and/or rare protox herbicides (acifluorfen). These herbicides are more toxic and persistent exerting a greater environmental impact; however, weed management is plant specific. In some cases of multiple herbicide resistance weed management practices are deep tillage (Peterson and Hulting, 2004).

In terms of human health, a qualitative assessment was conducted by comparing oral RfDs for these "other chemicals" (if available) to the proposed oral RfD for glyphosate. Based on the available acute and chronic oral RfDs for the majority of the "other chemicals", glyphosate's RfD is higher, therefore, making it more toxicologically benign, compared to the "other chemicals". The RfDs for the "other chemicals" are presented in table L-15. For further information and references to these RfD values, please see appendix L-5 of this technical report.

Table L-15. Summary of RfDs for "Other Chemicals"

Chemical Name	RfD (oral)
2,4-D	Acute dietary (Females 13-49 years of age): 0.025 mg/kg/day Acute dietary (General population including infants and children): 0.067 mg/kg/day Chronic dietary (All populations): 0.005 mg/kg/day
Acifluorfen	Chronic: 0.013 mg/kg/day
Amitrole	Not established
Atrazine	Acute Dietary: 0.1 mg/kg/day Intermediate and Chronic: 0.018 mg/kg/day
Benefin	Chronic: 0.3 mg/kg/day
Bromoxynil	Chronic: 0.015 mg/kg/day (
Clodinafop (clodinafop-propargyl)	Acute dietary (females 13-50 years of age): 0.05 mg/kg/day Acute dietary (general population including infants and children): 0.25 mg/kg/day Chronic dietary (all populations): 0.0003 mg/kg/day
Clopyralid	Chronic: 0.5 mg/kg/day
Cyanazine	Not available (NA)
Dicamba	Acute dietary (All populations): 1.0 mg/kg/day Chronic dietary (All populations): 0.45 mg/kg/day
Diquat (cation)	Chronic: 0.005 mg/kg/day
Ethalfluralin	Chronic: 0.04 mg/kg/day
Fenoxaprop (fenoxaprop-ethyl)	Chronic: 0.0025 mg/kg/day
Flucarbazone (flucarbazone-sodium)	Acute: 3.0 mg/kg/day Chronic: 0.36 mg/kg/day
Fluchloralin	NA
MCPA	Acute (General population): 0.05 mg/kg/day Acute (Females 13-50 years old): 0.04 mg/kg/day Chronic: 0.0044 mg/kg/day
Metribuzin	Chronic dietary: 0.013 mg/kg/day
Metsulfuron (metsulferon methyl	Chronic: 0.3 mg/kg/day
MSMA	Acute: 0.1 mg/kg/day Chronic: 0.03 mg/kg/day
Paraquat (cation)	Chronic: 0.0045 mg/kg/day
Pendimethalin	Chronic: 0.10 mg/kg/day
Simazine	Acute dietary (females 13-49 years of age): 0.3 mg/kg/day Chronic dietary (all populations): 0.018 mg/kg/day

Table L-15. Summary of RfDs for "Other Chemicals"

Chemical Name	RfD (oral)
Thifensulfuron (thifensulfuron methyl)	Acute dietary (Females 13-50 years of age): 1.59 mg/kg/day Chronic dietary (All populations): 0.20 mg/kg/day
Tralkoxydim	Acute: 0.3 mg/kg/day Chronic: 0.005 mg/kg/day
Triallate	Acute (General population including infants and children): 0.60 mg/kg/day Acute (Females 15-30 years): 0.05 mg/kg/day Chronic noncancer: 0.025 mg/kg/day
Triasulfuron	Chronic: 0.01mg/kg/day
Tribenuron (tribenuron methyl)	Chronic: 0.008 mg/kg/day Acute: 0.20 mg/kg/day
Trichlopyr	Chronic: 0.05 mg/kg/day
Trietazine	NA
Trifluralin	Chronic: 0.024 mg/kg/day

3.4 Risk Characterization

3.4.1 Overview

As discussed in section 3.2, the general public could be exposed to herbicides used on GT alfalfa if they consume crops that were grown near GT alfalfa fields. However, in section 3.1, it was demonstrated that EPA considers glyphosate to be of low acute toxicity by oral, dermal, and ocular routes of exposure, since all studies are classified as Toxicity Category III or IV. Furthermore, an acute inhalation study was waived by EPA because glyphosate is a nonvolatile solid and the studies conducted on the EUP formulation are considered sufficient. In terms of subchronic and chronic toxicity, one of the more occasional effects of exposure to glyphosate is reduced body weight gain. Other general and nonspecific signs of toxicity from subchronic and chronic exposure to glyphosate include changes in liver weight, blood chemistry (could suggest mild liver toxicity), and liver pathology (USDA, 2003). Glyphosate is not a carcinogen and has been classified by EPA as a Group E carcinogen (evidence of noncarcinogenicity for humans) (U.S. EPA, 2006, 1993).

3.4.2 Risk Characterization

To determine if any population subgroup is at risk of adverse effects associated with glyphosate, estimated exposure doses are compared with a health benchmark specific to glyphosate. As discussed in section 3.3, the recommended oral RfD for acute and chronic exposure scenarios for glyphosate is 2 mg/kg of body weight per day. This means that individuals with oral exposure doses equal to or less than 2 mg/kg of body weight per day should not be at risk of adverse effects associated with exposure to glyphosate. The risk metric used to determine if individuals are at risk of adverse effects is the HQ. The HQ is the ratio of the estimated exposure dose to the

chemical-specific health benchmark (e.g., RfD) (See equation 3.4.2). If the HQ is estimated to be less than 1, no adverse effects are expected as a result of exposure to the chemical of concern. If the HQ is much greater than 1, adverse health effects are possible. In a screening level risk assessment, an HQ exceeding 1 does not necessarily indicate that adverse effects are certain to occur. Since glyphosate is considered a Group E carcinogen (i.e., signifies noncarcinogenicity in humans) (U.S. EPA, 1993), an analysis of cancer risk was not conducted.

Equation L-14

$$HQ = \frac{Exposure}{RfD}$$

Where:

HQ	=	Hazard quotient (unitless)
Exposure	=	Estimated exposure dose (mg/kg bw/day)
RfD	=	Reference dose (mg/kg bw/day)

3.4.2.1 Risk Characterization for Acute Oral Exposure

Acute exposure estimates for adults (20-39 years), the elderly (70+ years), and infants (under 1 year in age) exposed to glyphosate-contaminated fruits and vegetables were presented in section 3.2. Results are summarized in table L-16 and in worksheet 13 in the calculations spreadsheet submitted with this report. Also, please refer to the calculations worksheet submitted with this report for further explanation of exposure estimate calculations.

Table L-16. Acute Exposure Screening Estimates by Age Group and Scenario (in mg/kg BW per day)

Scenario	Age Group	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Fruit	Adults	2.63E-02	0.00E+00	1.25E+00	1
Fruit	Elderly	4.17E-02	1.25E-02	4.50E-01	2
Fruit	Infants	2.09E-01	0.00E+00	6.32E+00	3
Vegetable	Adults	3.18E-01	1.85E-01	4.61E+00	4
Vegetable	Elderly	3.66E-01	2.22E-01	5.11E+00	5
Vegetable	Infants	6.12E-01	0.00E+00	1.21E+01	6

Acute exposure estimates were compared to the acute oral RfD of 2 mg/kg of body weight per day. Results are presented in table L-17. Please refer to the calculations worksheet submitted with this report for further explanation of HQ calculations.

Table L-17. Screening HQs by Age Group and Scenario

Scenario	Age Group	Central Estimate (in mg/kg BW per day)	Lower Estimate (in mg/kg BW per day)	Upper Estimate (in mg/kg BW per day)	RfD (in mg/kg BW per day)	Worksheet
Fruit	Adults	0.01	0.00	0.62	2	14
Fruit	Elderly	0.02	0.01	0.23	2	
Fruit	Infants	0.10	0.09	3.16	2	
Vegetable	Adults	0.16	0.09	2.30	2	
Vegetable	Elderly	0.18	0.11	2.55	2	
Vegetable	Infants	0.31	0.00	6.07	2	

3.4.2.2 Risk Characterization for Chronic Oral Exposure

Chronic exposure estimates for adults (20-39 years), the elderly (70+ years), and infants (under 1 year) exposed to glyphosate-contaminated fruits and vegetables were presented in section 3.2. Results are summarized in table L-18 and in worksheet 13 in the calculations spreadsheet submitted with this report. Also, please refer to the calculations worksheet submitted with this report for further explanation of exposure estimate calculations.

Table L-18. Chronic Exposure Screening Estimates by Age Group and Scenario (in mg/kg BW per day)

Scenario	Age Group	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Fruit	Adults	1.44E-02	0.00E+00	6.83E-01	7
Fruit	Elderly	2.29E-02	6.82E-03	2.46E-01	8
Fruit	Infants	1.14E-01	0.00E+00	3.46E+00	9
Vegetable	Adults	1.74E-01	1.01E-01	2.52E+00	10
Vegetable	Elderly	2.00E-01	1.22E-01	2.80E+00	11
Vegetable	Infants	3.35E-01	0.00E+00	6.65E+00	12

Chronic oral exposure estimates were compared to the chronic oral RfD of 2 mg/kg of body weight per day. Results are presented in table L-19. HQs above 1 are presented in bold type. Please refer to the calculations worksheet submitted with this report for further explanation of HQ calculations.

Table L-19. Screening HQs by Age Group and Scenario

Scenario	Age Group	Central Estimate (in mg/kg bw/day)	Lower Estimate (in mg/kg bw/day)	Upper Estimate (in mg/kg bw/day)	RfD (in mg/kg bw/day)	Worksheet
Fruit	Adults	0.01	0.00	0.34	2	14
Fruit	Elderly	0.01	0.00	0.12	2	
Fruit	Infants	0.06	0.00	1.73	2	
Vegetable	Adults	0.09	0.05	1.26	2	
Vegetable	Elderly	0.10	0.06	1.40	2	
Vegetable	Infants	0.17	0.00	3.32	2	

3.4.3 Discussion

The EPA (1993) RED for glyphosate included a dietary risk assessment in which it was determined that non-nursing infants were at highest risk of potential adverse effects associated with glyphosate exposure. EPA used tolerance level residues to estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. The TMRC for the U.S. population from food uses of glyphosate was 0.025 mg/kg/day (or 1.2 percent of the 2 mg/kg/day RfD). Non-nursing infants less than one year old had a TMRC of 0.058 mg/kg/day (or 2.9 percent of the RfD). This analysis was designed with conservative assumptions most likely result in an extremely protective estimate of exposure and risk. However, there was little commodity-specific consumption data at the time of the analysis, which might result in a less protective estimate. In its 2006 risk assessment for specific uses of glyphosate on Indian mulberry and dried peas, EPA used a proprietary dietary exposure and risk assessment model, DEEM-FCID™ to complete the dietary analysis for the general public. EPA only conducted a chronic dietary analysis and found that the highest exposed group, also infants under one year of age, was only exposed at 7 percent of the health benchmark used in the analysis. The results suggested that even the highest exposed group is not at risk of adverse effects (EPA, 2006).

The present analysis considers the possibility that any type of fruit or vegetable could be contaminated by glyphosate. As explained in section 3.2, central, upper, and lower estimates of consumption rates were used to estimate exposure and risk for adults, infants, and the elderly. It is anticipated that the results of this analysis are highly conservative for several reasons. First, the upper bound exposure and risk estimates are based on fruit and vegetable consumption rates characteristic of the 100th percentile of the population. In addition, in assuming a spray drift of one for all scenarios, this analysis assumes that fruits and vegetables will have the same residue of glyphosate as the GT alfalfa will. Application rates are specific to herbicides used to treat GT alfalfa fields, which is not meant for human consumption, as opposed to rates specific to fruits and vegetables. Acute and chronic scenarios assume that fruits and vegetables growing in nearby fields will be contaminated at the same level; however this is a highly conservative and in most cases unlikely scenario.

3.5 Summary of Findings

The use of currently registered pesticide products containing glyphosate in accordance with the labeling will not pose unreasonable risks or adverse effects to humans or the environment. It is a violation of federal law for any person to apply a registered pesticide in a manner inconsistent with its label. In general, the herbicidal activity of glyphosate is due primarily to a metabolic pathway that does not occur in humans or other animals, and, thus, this mechanism of action is not directly relevant to the human health risk assessment. EPA considers glyphosate to be of low acute toxicity by oral, dermal, and ocular routes of exposure, since all studies are classified as Toxicity Category III or IV. Furthermore, an acute inhalation study was waived by EPA because glyphosate is a nonvolatile solid and the studies conducted on the EUP formulation are considered sufficient.

Acute oral exposure estimates from fruit ingestion for adults ranged from zero to 1.25E+00 mg/kg bw/day. For elderly people, acute oral exposure estimates from fruit ingestion ranged

from 1.25E-02 to 4.5E-01 mg/kg bw/day. For infants, acute oral exposure estimates from fruit ingestion ranged from zero to 6.32E+00 mg/kg bw/day.

Acute oral exposure estimates from vegetable ingestion for adults ranged from 1.85E-01 to 4.61E+00 mg/kg bw/day. For elderly people, acute oral exposure estimates from vegetable ingestion ranged from 2.22E-01 to 5.11E+00 mg/kg bw/day. For infants, acute oral exposure estimates from vegetable ingestion ranged from zero to 1.21E+01 mg/kg bw/day.

Central and lower HQ estimates were all under 1. Some of the upper estimate screening HQs do exceed 1, but as discussed below these are based on very conservative assumptions for estimates of exposure and, for the acute assessment, are based on the highly conservative assumption of a chronic RfD for acute toxicity. The age group with the highest exposure is infants under one year of age, which is consistent with the EPA findings (U.S. EPA, 2006, 1993). The upper estimate screening HQ for infants with acute exposure to fruit was approximately 3. The upper estimate screening HQs for all age groups with acute exposure to vegetables ranged from approximately 2 to 6. Due to the screening level nature of this assessment, APHIS believes that the actual result in HQs from the implementation of the Preferred Alternative or Isolation/Geographic Restriction Alternative would be less than 1. The upper estimates of risk are based on highly conservative fruit and vegetable intake rates and exposure assumptions. Furthermore, the use of a chronic toxicity RfD for assessing acute toxicity is also conservative given (1) acute RfDs typically are much higher—usually by more than an order of magnitude—than chronic RfDs, and (2) EPA has concluded that that no relevant toxic effects are expected to result from single-dose oral exposure to glyphosate.

In terms of subchronic and chronic toxicity, one of the more consistent effects of high levels of exposure to glyphosate is reduced body weight gain at high doses. Other effects observed from subchronic and chronic exposure to glyphosate include changes in liver weight, blood chemistry (could suggest mild liver toxicity), and liver pathology (USDA, 2003). Glyphosate is not considered a mutagen, developmental or reproductive toxicant, or carcinogen and has been classified by EPA as a Group E carcinogen (evidence of noncarcinogenicity for humans) (U.S. EPA, 2006, 1993).

Chronic oral exposure estimates from fruit ingestion for adults ranged from zero to 6.83E-01 mg/kg bw/day. For elderly people, chronic oral exposure estimates from fruit ingestion ranged from 6.82E-03 to 2.46E-01 mg/kg bw/day. For infants, chronic oral exposure estimates from fruit ingestion ranged from 0 to 3.46E+00 mg/kg bw/day.

Chronic oral exposure estimates from vegetable ingestion for adults ranged from 1.01E-01 to 2.52E+00 mg/kg bw/day. For elderly people, chronic oral exposure estimates from vegetable ingestion ranged from 1.22E-01 to 2.80E+00 mg/kg bw/day. For infants, chronic oral exposure estimates from vegetable ingestion ranged from 0 to 6.65E+00 mg/kg bw/day.

Central and lower screening HQ estimates were all less than 1 . Some of the upper estimate screening HQs do exceed 1, but are based on very conservative assumptions for estimates of exposure. The age group at highest risk is infants under one year of age, which is consistent with the EPA findings (1993, 2006). The upper estimate screening HQ for infants with chronic

exposure to fruit was approximately 2. The upper estimate screening HQs for all age groups with chronic exposure to vegetables ranged from approximately 1 to 3. Due to the screening level nature of this assessment, APHIS believes that the actual result in HQs from the implementation of the Preferred Alternative or Isolation/Geographic Restriction Alternative would be less than 1. The upper estimates of risk are based on highly conservative fruit and vegetable intake rates.

This screening-level analysis of exposure to the general public considers the possibility that any type of fruit or vegetable could contain residues of glyphosate. Central, upper, and lower estimates of consumption rates were used to estimate exposure and risk for adults, infants, and the elderly. The results of this analysis are based on a screening-level assessment used highly conservative assumptions that when combined do not reflect actual risk. These assumptions include:

- The upper-bound exposure and risk estimates are based on fruit and vegetable consumption rates characteristic of the 100th percentile of the population (the maximum consumption rate).
- In assuming a spray drift of 1 for all scenarios, this analysis assumes that all of the overspray deposits on the fruits and vegetables as if they were sprayed directly, with no reduction due to dilution, dispersion, and removal by air and rain.
- Application rates are specific to herbicides used to treat GT alfalfa forage fields, which is not meant for human consumption, as opposed to rates specific to fruits and vegetables.
- This analysis assumes that 100 percent of the glyphosate residue remains on the produce, i.e., none is removed during washing or other processing.
- This analysis uses a chronic toxicity RfD for assessing acute toxicity, which will overestimate acute risk because (1) acute RfDs typically are much higher—usually by more than an order of magnitude—than chronic RfDs, and (2) EPA has concluded that that no relevant toxic effects are expected to result from single-dose oral exposure to glyphosate.

In summary, APHIS recognizes that the Preferred Alternative and Isolation/Geographic Restriction Alternative are unlikely to have impacts similar to the results of the assessment, and the assessment is intended to disclose very conservative potential impacts. Due to the screening level nature of this assessment, APHIS believes that the actual result from the implementation of the Preferred Alternative or Isolation/Geographic Restriction Alternative would not result in adverse effects as a result of exposure to the chemical of concern. Based on the results of this screening-level assessment, APHIS has determined a detailed assessment is not needed.

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Wester, R.C., Melendres, J., Sarason, R., Mcmaster, J., and Maibach, H.I. (1991). Glyphosate skin binding, absorption, residual tissue distribution, and skin decontamination. *Fundam Appl Toxicol*. 16(4):725−732. *(As cited in USDA, 2003).*

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WHO. (1986). Report of the second joint meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues, FAO Meeting Report No. PL/1965/10; WHO/Food Add./26.65. Available online at http://www.inchem.org/documents/jmpr/jmpmono/v86pr08.htm. (Accessed 8/5/2010).

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Appendix L-2. Literature Search

1.0 Literature Search Strategy

1.1 Purpose

Primary sources of data were obtained from the following three documents: EPA 1993 RED on glyphosate (U.S. EPA, 1993); the EPA Glyphosate Human Health Risk Assessment for Proposed Use on Indian Mulberry and Amended Use on Pea, Dry (U.S. EPA, 2006); and the USDA, Forest Service 2003 human health and ecological risk assessment on glyphosate (USDA, 2003). The purpose of this literature search, therefore, was to locate additional references about the health and safety risks from increased glyphosate and other chemical use on humans (exclusive of field workers). Several DIALOG databases were searched, and Google, and Google Scholar search engines supplemented the DIALOG search. References were selected from the extensive list of literature based on requesting the abstracts and determining if the open literature data were not included in the three primary documents listed below or provided contrary or controversial information to these documents.

The following DIALOG databases will be included in the search:

File 5: BIOSIS
File 34: SciSearch
File 40: Enviroline
File 76: Environmental Sciences
File 98: General Science Abstracts
Abstracts
File 154: MEDLINE
File 245: WATERNET™
File 266: Federal Research In Progress (FEDRIP)
File 5: BIOSIS
File 34: SciSearch

File 6: NTIS
File 41: Pollution Abstracts
File 72: EMBASE
File 79: Aqualine
File 117: Water Resources
File 144: PASCAL
File 156:ToxFile
File 250: CAB Abstracts
File 399: CA SEARCH®: Chemical

File 6: NTIS
File 41: Pollution Abstracts

Descriptions of these files are available at http://library.dialog.com/bluesheets/.

1.2 Scope of Search

The search will focus on references published after 1990. A reference list with abstracts will be screened for relevance. English language only publications will be retrieved.

1.3 Strategy Overview

A list of search parameters is listed below.

1.4 Synonyms

- Glyphosate
- Glyphosate, isopropylamine salt
- Glyphosate, sodium salt
- Glyphosate, potassium
- Glyphosate, ammonium
- Glyphosate, sulfosate
- *N*-(phosphonomethyl) glycine
- Roundup®
- Roundup Ultra®
- Honcho®

1.5 Keywords

- Acute
- Alfalfa
- Allowable daily intake
- Cancer*
- Carcino*
- Chronic
- Crop
- Degradation
- Derma*
- Developmental
- Dietary risk
- Dose
- Emission
- Endpoint
- Environmental Health
- Embryo
- Environmental impacts
- Exposure(s)
- Eye
- Fertility
- Health effect(s)
- Human health risk
- Incidental
- Ingest*
- Inhal*
- Inhibition
- Irritation
- Leach*
- Metabo*
- Mutagen*
- Neuro*
- Nontarget crops
- Persistence
- Reproducti*
- Residue
- Risk
- Sensitization
- Spray drift
- Subchronic
- Terato*
- Tolerance
- Toxic*
- Usage patterns

1.6 Submission of Citations for Approval

Using reference management software, pooled information obtained from the various bibliographic databases will be screened to remove duplicates. Additionally, ICF will review the list prior to submission and eliminate any irrelevant citations. Information provided to USDA will include the following (when available):

Title. Publication Year.

1.7 Literature Search Results:

TITLES FROM VARIOUS COMBINATIONS OF THE SEARCH SETS

22/6/3 (Item 3 from file: 154)
14946077 PMID: 12507058
An analysis of *glyphosate* data from the California Environmental Protection Agency Pesticide Illness Surveillance Program.
2002

22/6/20 (Item 20 from file: 154)
14535687 PMID: 11890463
Current methods for assessing *safety* of genetically modified crops as exemplified by data on *Roundup* Ready soybeans.
Jan-Feb *2002*

22/6/21 (Item 21 from file: 154)
16416941 PMID: 15929894
Differential effects of *glyphosate* and *roundup* on *human* placental cells and aromatase.
Jun *2005*

22/6/27 (Item 27 from file: 50)
0008562363 CAB Accession Number: 20043013531
The effect of spray particle size and distribution on drift and efficacy of herbicides.
Publication Year: 2004

22/6/28 (Item 28 from file: 154)
14263603 PMID: 11564623
An exploratory analysis of the effect of pesticide *exposure* on the risk of spontaneous abortion in an Ontario farm population.
Aug *2001*

22/6/32 (Item 32 from file: 73)
0081488433 EMBASE No: 2006551723
The farm family *exposure* study: Acquavella et al. respond [3]
November 1, 2006

22/6/33 (Item 33 from file: 73)
0080877664 EMBASE No: 2005522322
Farm Family *Exposure* Study: Methods and recruitment practices for a biomonitoring study of pesticide *exposure*
November 1, 2005

22/6/34 (Item 34 from file: 73)
0081234988 EMBASE No: 2006297170
Gliomas and farm pesticide *exposure* in men: The upper midwest health study
December 1, 2004

22/6/35 (Item 35 from file: 162)
0005035481 CAB Accession Number: 20053018188
Glyphosate.
Publication Year: 2004

22/6/37 (Item 37 from file: 154)
16233423 PMID: 15694458
A glyphosate-based pesticide impinges on transcription.
Feb 15 *2005*

22/6/38 (Item 38 from file: 154)
16165018 PMID: 15862083
Glyphosate *poisoning*.
2004

22/6/39 (Item 39 from file: 73)
0080634337 EMBASE No: 2005278629
Glyphosate results revisited (multiple letters) [2]
June 1, 2005

22/6/42 (Item 42 from file: 154)
15338586 PMID: 12937207
Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.
Sep *2003*

22/6/43 (Item 43 from file: 73)
0081540797 EMBASE No: 2006604398
In utero pesticide *exposure* and childhood morbidity
January 1, 2007

22/6/44 (Item 44 from file: 76)
0001821739 IP ACCESSION NO: 6653001
Mechanism of *toxicity* of commercial *glyphosate* formulatons: How important is the surfactant?
PUBLICATION DATE: *2005*

22/6/45 (Item 45 from file: 73)
0080120735 EMBASE No: 2004304381
Non-Hodgkin's lymphoma among asthmatics *exposed* to pesticides
August 20, 2004

22/6/49 (Item 49 from file: 73)
0080171096 EMBASE No: 2004353558
Patterns of pesticide use and their determinants among wives of farmer pesticide applicators in the agricultural health study
August 1, 2004

22/6/50 (Item 50 from file: 162)
0005222326 CAB Accession Number: 20073099434
Pesticide contamination inside farm and nonfarm homes.
Publication Year: 2005

22/6/51 (Item 51 from file: 73)
0081560810 EMBASE No: 2006624680
Pesticides and adult respiratory outcomes in the agricultural health study
ISSUE TITLE: Living in a Chemical World: Framing the Future in Light of the Past
September 1, 2006

22/6/52 (Item 52 from file: 73)
0082048526 EMBASE No: 2007489590
Pesticide *dose* estimates for children of Iowa farmers and non-farmers
November 1, 2007

22/6/56 (Item 56 from file: 154)
26616354 PMID: 18320729
Pesticide-related *dermatitis* in Saku district, Japan, 1975-2000.
Jan-Mar *2008*

22/6/59 (Item 59 from file: 73)
0080634359 EMBASE No: 2005278651
Roundup revelation. Weed killer adjuvants may boost *toxicity*
June 1, 2005

22/6/61 (Item 61 from file: 73)
0081488432 EMBASE No: 2006551722
Suggested corrections to the farm family *exposure* study [2]
November 1, 2006

22/6/62 (Item 62 from file: 10)
4632422 43919222 Holding Library: AGL
Time- and *Dose*-Dependent Effects of *Roundup* on *Human* Embryonic and Placental Cells
2007
URL: http://dx.doi.org/10.1007/s00244-006-0154-8

22/6/64 (Item 64 from file: 10)
4638864 43876156 Holding Library: AGL
Toxicity assessment of the main pesticides used in Costa Rica
2007
URL: http://dx.doi.org/10.1016/j.agee.2006.05.010

28/6/3 (Item 3 from file: 154)
26532387 PMID: 18358975
Acute pancreatitis caused by severe *glyphosate*-surfactant oral *intoxication*.
Mar *2008*

28/6/5 (Item 5 from file: 55)
18548217 BIOSIS NO.: 200510242717
Agricultural pesticide-related *poison* in Italy: Cases reported to the *Poisoning* Control Center of Milan in 2000-2001
2004

28/6/8 (Item 8 from file: 154)
25632929 PMID: 17984146
Alteration of estrogen-regulated gene expression in *human* cells induced by the agricultural and horticultural herbicide *glyphosate*.
Sep *2007*

28/6/14 (Item 14 from file: 73)
0081251566 EMBASE No: 2006313832
Analysis of 8000 hospital admissions for *acute* *poisoning* in a rural area of Sri Lanka
May 1, 2006

28/6/20 (Item 20 from file: 55)
18056718 BIOSIS NO.: 200400427507
Avoiding the penalties of *spray* *drift* with a practical look at *glyphosate*
2004

28/6/30 (Item 30 from file: 154)
16614216 PMID: 16190155
Biomonitoring for *farm* *families* in the *farm* *family* *exposure*study.
2005

28/6/33 (Item 33 from file: 154)
14660317 PMID: 12060842
Birth defects, season of conception, and sex of *children* born to pesticide applicators living in the Red River Valley of Minnesota, USA.
Jun *2002*

28/6/45 (Item 45 from file: 154)
13704636 PMID: 10958131
Clinical presentations and prognostic factors of a *glyphosate* -surfactant herbicide *intoxication*: a review of 131 cases.
Aug *2000*

28/6/46 (Item 46 from file: 55)
0019973330 BIOSIS NO.: 200800020269
Clinical outcomes after suicidal *ingestion* of *glyphosate* surfactant herbicide: Severity of *intoxication* according to amount *ingested*
2007

28/6/48 (Item 48 from file: 154)
15525131 PMID: 14705857
Comment on "An analysis of *glyphosate* data from the California Environmental Protection Agency Pesticide Illness Surveillance Program".
2003

28/6/50 (Item 50 from file: 10)
4371758 43771446 Holding Library: AGL
Comparative effects of the *Roundup* and *glyphosate* on mitochondrial oxidative phosphorylation
2005

28/6/51 (Item 51 from file: 73)
0081478551 EMBASE No: 2006541781
Comparative *genotoxicity* of the herbicides *Roundup*, Stomp and Reglone in plant and mammalian test systems
November 1, 2006

28/6/54 (Item 54 from file: 154)
16715180 PMID: 16315092
A comparative risk assessment of genetically engineered, *mutagenic*, and conventional wheat production systems.
Dec *2005*

28/6/59 (Item 59 from file: 55)
17952638 BIOSIS NO.: 200400323402
Comparison of the effect of *Roundup* Ultra 360 SL pesticide and its active compound *glyphosate* on *human* erythrocytes
2004

28/6/74 (Item 74 from file: 55)
0019750321 BIOSIS NO.: 200700410062
Cysteine turnover in *human* cell lines is influenced by *glyphosate*
2007

28/6/78 (Item 78 from file: 154)

25632485 PMID: 17882442
Defense against *dermal* *exposures* is only *skin* deep: significantly increased penetration through slightly damaged *skin*.
Nov *2007*

28/6/79 (Item 79 from file: 55)
0019648010 BIOSIS NO.: 200700307751
Differential effects of *glyphosate* and *roundup* in gene expression of *human* peripheral blood mononuclear cells: Implications for hematological *carcinogenesis*.
2007

28/6/80 (Item 80 from file: 156)
4011073 NLM Doc No: 15929894
Differential effects of *glyphosate* and *roundup* on *human* placental cells and aromatase.
Jun *2005*
28/6/87 (Item 87 from file: 154)
15857617 PMID: 15240034
Determination of *glyphosate* in biological fluids by 1H and 31P NMR spectroscopy.
Jul 16 *2004*

28/6/88 (Item 88 from file: 154)
15169562 PMID: 12731658
Determination of the herbicide *glyphosate* and its *metabolite* in biological specimens by gas chromatography-mass spectrometry. A case of *poisoning* by *roundup* herbicide.
Apr *2003*

28/6/91 (Item 91 from file: 73)
0082318049 EMBASE No: 2008142852
Dietary *exposure* to pesticide residues in Yaounde: The Cameroonian total diet study
April 1, 2008

28/6/92 (Item 92 from file: 154)
13858726 PMID: 11139167
Development of California Public Health Goals (PHGs) for chemicals in drinking water.
Sep-Oct *2000*

28/6/107 (Item 107 from file: 10)
3899354 22437401 Holding Library: AGL
Influence of paraquat, *glyphosate*, and cadmium on the activity of some serum enzymes and protein electrophoretic behavior (in vitro)
2001

28/6/108 (Item 108 from file: 55)
16070131 BIOSIS NO.: 200100241970
Effect of pesticides and CdCl2 on serum enzyme and protein electrophoretic behaviour (in vitro)
2000

28/6/109 (Item 109 from file: 162)
0004952937 CAB Accession Number: 20033205456
The effects of refining consumer *exposure* assessments of *glyphosate*.
Book Title: The BCPC International Congress: Crop Science and Technology, Volumes 1 and 2. Proceedings of an international congress held

at the SECC, Glasgow, Scotland, UK, 10-12 November 2003
Publication Year: 2003

28/6/110 (Item 110 from file: 10)
4211069 43658629 Holding Library: AGL
Effects of refining predicted *chronic* *dietary* intakes of pesticide residues: a case study using *glyphosate*
2004

28/6/119 (Item 119 from file: 154)
16176902 PMID: 17134388
Environmental and human health impacts of growing genetically modified herbicide-tolerant sugar beet: a life-cycle assessment.
Jul *2004*

28/6/124 (Item 124 from file: 154)
17063768 PMID: 16749554
Can early hemodialysis affect the outcome of the *ingestion* of *glyphosate* herbicide?
2006

28/6/126 (Item 126 from file: 154)
26532351 PMID: 18358936
The early prognostic factors of *glyphosate*-surfactant *intoxication*.
Mar *2008*

28/6/127 (Item 127 from file: 73)
0078416702 EMBASE No: 2001022513
Erratum: Rapid lethal *intoxication* caused by the herbicide *glyphosate* -trimesium (touchdown) (*Human* & Experimental *Toxicology* vol. 18(12) (2000) (735-737))
December 1, 2000

28/6/129 (Item 129 from file: 55)
0019787949 BIOSIS NO.: 200700447690
Evaluation of DNA damage in an Ecuadorian population *exposed* to *glyphosate*
2007

28/6/131 (Item 131 from file: 156)
3686287 NLM Doc No: 11564623
An exploratory analysis of the effect of pesticide *exposure* on the risk of spontaneous abortion in an Ontario farm population.
Aug *2001*

28/6/132 (Item 132 from file: 154)
16811634 PMID: 16357597
Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring.
Jan *2006*

28/6/135 (Item 135 from file: 154)
14733906 PMID: 12148884
Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies.
May *2002*

28/6/140 (Item 140 from file: 55)
17061934 BIOSIS NO.: 200300020653

Farm *family* *exposure* study: Biomonitoring results for *glyphosate*.
2002

28/6/142 (Item 142 from file: 55)
17543919 BIOSIS NO.: 200300498947
Farm *exposure* to pesticides and glioma in women.
2003

28/6/150 (Item 150 from file: 154)
15655427 PMID: 14998747
Glyphosate biomonitoring for *farmers* and their families: results from the *Farm* *Family* *Exposure* Study.
Mar *2004*

28/6/151 (Item 151 from file: 154)
15806818 PMID: 15182708
Glyphosate-based pesticides affect cell cycle regulation.
Apr *2004*

28/6/154 (Item 154 from file: 154)
15847227 PMID: 15228468
Glyphosate herbicide formulation: a potentially lethal ingestion.
Jun *2004*

28/6/155 (Item 155 from file: 55)
19155868 BIOSIS NO.: 200600501263
Glyphosate-induced antioxidant imbalance in HaCaT: The protective effect of vitamins C and E
2006

28/6/157 (Item 157 from file: 156)
3973750 NLM Doc No: 15862083
Glyphosate *poisoning*.
2004

28/6/158 (Item 158 from file: 73)
0079472981 EMBASE No: 2003178348
Glyphosate *poisoning* - A rare case of herbicide *poisoning*
July 1, 2002

28/6/160 (Item 160 from file: 10)
4823604 44034732 Holding Library: AGL
Glyphosate-resistant crops: adoption, use and future considerations
2008
URL: http://dx.doi.org/10.1002/ps.1501

28/6/162 (Item 162 from file: 55)
18724863 BIOSIS NO.: 200600070258
Glyphosate surfactant herbicide-induced *acute* renal failure
2005

28/6/164 (Item 164 from file: 73)
0080873358 EMBASE No: 2005518013
GMO: *Human* *health* *risk* assessment
August 1, 2005

28/6/169 (Item 169 from file: 10)
4795875 44017629 Holding Library: AGL
Genotoxic Potential of *Glyphosate* Formulations: Mode-of-Action

Investigations
2008
URL: http://dx.doi.org/10.1021/jf072581i

28/6/170 (Item 170 from file: 154)
26379341 PMID: 18084044
A gene-shuffled *glyphosate* acetyltransferase protein from Bacillus licheniformis (GAT4601) shows no evidence of allergenicity or *toxicity*.
Apr *2008*

28/6/175 (Item 175 from file: 10)
4823622 44034750 Holding Library: AGL
Herbicides, *glyphosate* resistance and *acute* mammalian *toxicity*: simulating an environmental effect of *glyphosate*-resistant weeds in the USA
2008
URL: http://dx.doi.org/10.1002/ps.1497

28/6/180 (Item 180 from file: 73)
0078408708 EMBASE No: 2001014519
Impact of pesticides use on *human* health in Mexico: A review
December 1, 2000

28/6/181 (Item 181 from file: 10)
3979215 23250194 Holding Library: AGL
Implications of *glyphosate* *toxicology* and *human* biomonitoring data for epidemiologic research
2001

28/6/186 (Item 186 from file: 73)
0081657997 EMBASE No: 2007091481
Inferring past pesticide *exposures*: A matrix of individual active ingredients in *home* and garden pesticides used in past decades
February 1, 2007

28/6/190 (Item 190 from file: 156)
3850884 NLM Doc No: 12937207
Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.
Sep *2003*

28/6/193 (Item 193 from file: 55)
0019466064 BIOSIS NO.: 200700125805
In utero pesticide *exposure* and childhood morbidity
2007

28/6/194 (Item 194 from file: 154)
13655777 PMID: 10933758
In vitro studies of cellular and molecular developmental *toxicity* of adjuvants, herbicides, and fungicides commonly used in Red River Valley, Minnesota.
Jul 28 *2000*

28/6/195 (Item 195 from file: 55)
18581240 BIOSIS NO.: 200510275740
In vitro evaluation of *glyphosate*-induced DNA damage in fibrosarcoma cells HT1080 and Chinese hamster ovary (CHO) cells.
2004

28/6/196 (Item 196 from file: 154)
14266614 PMID: 11569770
Investigation of the herbicide *glyphosate* and the plant growth regulators chlormequat and mepiquat in cereals produced in Denmark.
Oct *2001*

28/6/206 (Item 206 from file: 55)
19253044 BIOSIS NO.: 200600598439
Molecular and cellular effects of *glyphosate* on *human* lymphocytes: Implications for non-Hodgkin's lymphoma.
2006

28/6/212 (Item 212 from file: 55)
17262052 BIOSIS NO.: 200300220771
Non-specific alteration of steroidogenesis in MA-10 Leydig cells by supra-physiological concentrations of the surfactant in *Roundup*(R) herbicide.
2003

28/6/213 (Item 213 from file: 156)
190707 NLM Doc No: DART/TER/4001875 Sec. Source ID: DART/TER/4001875
Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications.
2004

28/6/226 (Item 226 from file: 40)
00640398 ENVIROLINE NUMBER: 03-07730
Organophosphorus Pesticide *Exposure* of Urban and Suburban Preschool *Children* with Organic and Conventional Diets
Mar 03

28/6/227 (Item 227 from file: 154)
16224136 PMID: 15683179
Oral bioavailability of *glyphosate*: studies using two intestinal cell lines.
Jan *2005*

28/6/228 (Item 228 from file: 154)
26643404 PMID: 18442254
Oxidative damage mediated by herbicides on yeast cells.
May 28 *2008*

28/6/235 (Item 235 from file: 154)
14119755 PMID: 11391760
Parkinsonism after glycine-derivate *exposure*.
May *2001*

28/6/238 (Item 238 from file: 154)
17095239 PMID: 16787817
Parenteral *glyphosate*-surfactant herbicide *intoxication*.
Jul *2006*

28/6/246 (Item 246 from file: 154)
16487576 PMID: 16020099
Pesticide contamination inside farm and nonfarm *homes*.
Jul *2005*

28/6/247 (Item 247 from file: 154)
25071148 PMID: 17659274

Pesticide *dose* estimates for *children* of Iowa *farmers* and non-*farmers*.
Nov *2007*

28/6/249 (Item 249 from file: 73)
0080532622 EMBASE No: 2005176821
Pesticides and *human* health: Why public health officials should support a ban on non-essential residential use
March 1, 2005

28/6/253 (Item 253 from file: 73)
0080107139 EMBASE No: 2004291195
Pesticide *intoxications* in the Centre of Portugal: Three years analysis
July 16, 2004

28/6/254 (Item 254 from file: 154)
14961841 PMID: 12549246
Pesticide use and practices in an Iowa *farm* *family* pesticide *exposure* study.
Nov *2002*

28/6/255 (Item 255 from file: 73)
0082286261 EMBASE No: 2008100152
Pesticides and prostate *cancer*: A review of epidemiologic studies with specific agricultural *exposure* information
April 1, 2008

28/6/257 (Item 257 from file: 154)
25284275 PMID: 17976274
Pesticide regulation, utilization, and retailers' selling practices in Trinidad and Tobago, West Indies: current situation and needed changes.
Aug *2007*

28/6/259 (Item 259 from file: 154)
14540961 PMID: 11896679
Pesticide *Roundup* provokes cell division dysfunction at the level of CDK1/cyclin B activation.
Mar *2002*

28/6/263 (Item 263 from file: 154)
26291470 PMID: 18371753
Quantitative determination of *glyphosate* in *human* serum by 1H NMR spectroscopy.
Jan 15 *2008*

28/6/266 (Item 266 from file: 55)
16849926 BIOSIS NO.: 200200443437
A quantitative approach for estimating *exposure* to pesticides in the agricultural health study
2002

28/6/277 (Item 277 from file: 154)
25260805 PMID: 17915625
Roundup *intoxication* and a rationale for treatment.
Sep *2007*

28/6/284 (Item 284 from file: 154)
13617796 PMID: 10854122

Safety evaluation and risk assessment of the herbicide *Roundup* and its active ingredient, *glyphosate*, for *humans*.
Apr *2000*

28/6/288 (Item 288 from file: 154)
26557440 PMID: 18407393
Skin decontamination of *glyphosate* from *human* *skin* in vitro.
Jun *2008*

28/6/289 (Item 289 from file: 154)
15959003 PMID: 15362602
Skin *toxicity* from *glyphosate*-surfactant formulation.
2004

28/6/295 (Item 295 from file: 73)
0078595998 EMBASE No: 2001202299
The surveillance of agrichemical spraydrift incidents in New Zealand 1999-2000
June 29, 2001
28/6/311 (Item 311 from file: 144)
15662712 PASCAL No.: 02-0368723
The *toxicology* of herbicides
2001

28/6/312 (Item 312 from file: 73)
0080836676 EMBASE No: 2005481309
Toxicity tests: "inert" and active ingredients (multiple letters) [5]
October 1, 2005

28/6/313 (Item 313 from file: 55)
0019458363 BIOSIS NO.: 200700118104
Toxicity assessment of the main pesticides used in Costa Rica
2007

28/6/317 (Item 317 from file: 154)
17473895 PMID: 16984946
Urinary pesticide concentrations among *children*, mothers and fathers living in farm and non-farm households in iowa.
Jan *2007*

Appendix L-3. Summary of Toxicology Studies

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
Acute Toxicity				
Acute Dermal	Rabbit	Not provided	> 2 g/kg (Category III)	Birch et al., 1970 (MRID 00067039)
Acute Oral	Rat	Not provided	> 4,320 mg/kg (Category III)	Birch et al., 1970 (MRID 00067039)
Eye Irritation	Not provided	Not provided	Mild irritation, clears in 7 days (Category III)	Blaszcak, 1988c (MRID 41400603)
Dermal Irritation	Not provided	Not provided	Slight irritation (Category IV)	Blaszcak, 1988d (MRID 41400604)
Skin Sensitization	Not provided	Not provided	Negative	Auletta et al., 1983a (MRID 00137137), Auletta et al., 1983b (MRID 00137138), Maibach, 1982 (MRID 0013139), and Franz, 1983 (MRID 00137140)
Subchronic Toxicity				
90-Day Feeding	CD-1 Mice	0, 250, 500, or 2,500 mg/kg/day	NOEL: 500 mg/kg (both sexes) LOEL: 2,500 mg/kg (both sexes) Systemic toxicity Based on body weight gains	Street et al., 1980 (MRID 00036803)
13-Week Feeding	Mice	3,125, 6,250, 12,500, 25,000 or 50,000 ppm (Males: 507, 1,065, 2,273, 4,776 or 10,780 mg/kg/day; Females: 753, 1,411, 2,707, 5,846 or 11,977 mg/kg/day)	Decreased body weight at two highest dose levels in both sexes, increased relative heart, kidney, liver, lung, thymus, and testis weight for males, salivary glad lesions, no effects on food consumption, sperm motility or estrous cycle length	NCI, 1992
21-Day Dermal	New Zealand White Rabbits	10, 1,000, or 5,000 mg/kg/day	NOEL: 1,000 mg/kg/day (both sexes) LOEL: 5,000 mg/kg/day (both sexes)	Johnson et al., 1982 (MRID 00098460)

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
			Based on erythema, edema, food consumption, and serum changes	
6-Weeks, gelatin capsule administered orally	New Zealand Rabbits, male	1/10th or 1/100th of the LD_{50}	Decreased body weight, libido, ejaculate volume, sperm concentrations, semen initial fructose and semen osmolarity, increases in abnormal and dead sperm	Yousef et al., 1996
90-Day Feeding	Sprague-Dawley Rats	0, 1,000, 5,000, or 20,000 ppm	NOEL: < 1,000 ppm (both sexes) Systemic toxicity Based on serum changes and pancreatic lesions	Stout and Johnson, 1987, as cited in USDA 2003 (MRID 40559401) and Lankas et al., 1981 (MRID 00093879)
13-Week Feeding	Rat	3,125, 6,250, 12,500, 25,000, or 50,000 ppm (Males: 205, 410, 811, 1,678, or 3,393 mg/kg/day Females: 213, 421, 844, 1,690, or 3,393 or mg/kg/day)	Decreased body weight in males (20%) and females (5%) at the highest dose level, mild liver toxicity in both sexes at all time points, 20% decrease in sperm counts at two higher doses, longer estrous cycle at the highest dose, frequency of salivary glad lesions increases with dose level.	NCI, 1992
Chronic Toxicity				
One-Year Feeding	Beagle Dogs	0, 20, 100, or 500 mg/kg/day	NOEL: ≥ 500 mg/kg/day Systemic toxicity	Reyna, 1985 (MRID 00153374)
24-Month Feeding *U.S. EPA 1995[*FR* July 7, Vol 60, No. 130] indicates that the exposure duration was 18 months, not 24	CD Mice	1,000, 5,000, or 30,000 ppm (Males: 111-250, 519-1,264 or 3,465-7,220 mg/kg/day Females: 129-288, 690-1,322, or 4,232-9,859 mg/kg/day)	NOAEL: 5,000 ppm (750 mg/kg/day) Based on non-neoplastic chronic effects, body weights, histopathological changes and chronic interstitial necrosis, proximal tubule epithelial cell basophilia and hypertrophy of the kidneys	U.S. EPA, 1986, as cited in USDA 2003
2-Year Feeding (Carcinogenicity)	Sprague-Dawley Rats	0, 2,000, 8,000, or 20,000 ppm (Males: 0, 89, 362, or 940 mg/kg/day Females: 0, 113,	NOEL: 8,000 ppm (both sexes), Males: 362 mg/kg/day, Females: 457 mg/kg/day LOEL: 20,000 ppm (both sexes), Males: 940	Stout and Ruecker, 1990 (MRID 41643801)

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
		457 or 1,183 mg/kg/day)	mg/kg/day, Females: 1,183 mg/kg/day Systemic toxicity Based on body weight, cataracts and lens abnormalities, urinary pH, liver weight, liver weight/brain weight ratio	
26-Month Feeding	Sprague-Dawley Rats	0, 30, 100, or 300 ppm (Males: 0, 3, 10 or 31 mg/kg/day Females: 0, 3, 11, or 34 mg/kg/day)	NOEL: ≥ 300 ppm (both sexes); Males: 31 mg/kg/day, Females: 34 mg/kg/day Systemic toxicity Based on toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology	Lankas et al., 1981 (MRID 00093879)
Carcinogenicity				
18-Month Feeding	CD-1 Mice	0, 150, 750, or 4500 mg/kg/day	NOEL: 750 mg/kg/day LOEL: 4500 mg/kg/day Not carcinogenic based on body weight, hepatocellular hypertrophy or necrosis, interstitial nephritis, proximal tubule epithelial basophilia and hypertrophy, adenomas	Knezevich and Hogan, 1983 (MRID 00130406) and McConnel, 1985 (MRID 00150564)
2-Year Feeding (Chronic)	Sprague-Dawley Rats	Males: 0, 89, 362, or 940 mg/kg/day Females: 0, 113, 457 or 1183 mg/kg/day	Not carcinogenic based on incidences of adenomas	MRID 41648301
24-Month Feeding	Sprague-Dawley Rats	2000, 8,000, or 20,000 ppm (Males: 89, 362 or 940 mg/kg/day Females: 45, 113 or 1183 mg/kg/day)	NOAEL: 8000 ppm Based on body weight, cataracts and lens abnormalities, urinary tract pH, liver weight and inflammation of gastric mucosa	Stout and Ruecker, 1990
26-Month Feeding (Chronic)	Sprague-Dawley Rats	Males: 0, 3, 10, or 31 mg/kg/day Females: 0, 3, 11 or 34 mg/kg/day	Not carcinogenic based on incidences of carcinomas and tumors	Lankas et al., 1981 (MRID 00093879)
Developmental Toxicity				
Gavage on days	Dutch Belted	0, 75, 175, or	NOEL: ≥175 mg/kg/day	Rodwell et al.,

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
6-27 of gestation	Rabbits, pregnant	350 mg/kg/day		1980b (MRID 00046363)
Gavage on days 6-19 of gestation	Charles River COBS CD Rats, pregnant	0, 300, 1000, or 3500 mg/kg/day	NOEL: 1000 mg/kg/day LOEL: 3500 mg/kg/day Based on number of litters and fetuses with unossified sternebrae and fetal body weights	Rodwell et al., 1980a (MRID 00046362)
Continuously in diet for two successive generations	Sprague-Dawley Rats	0, 100, 500, or 1500 mg/kg/day	NOEL: 500 mg/kg/day LOEL: 1500 mg/kg/day Based on soft stools, food consumption, and body weight	Reyna, 1990 (MRID 41621501)
Continuously in diet for three successive generations	Sprague-Dawley Rats	0, 3, 10, or 30 mg/kg/day	NOEL: 10 mg/kg/day LOEL: 30 mg/kg/day Based on focal tubular dilation of kidney	Street, 1982 (MRID 00105995)
Maternal Toxicity				
Gavage on days 8-20 of gestation	New Zealand Rabbits	0, 100, 175, or 300 mg/kg/day	Maternal toxicity: 175 and 300 mg/kg/day Fetal toxicity: 300 mg/kg/day Based on diarrhea, fecal output, food intake, body weight and ossification	Moxon, 1996b
Gavage on days 6-27 of gestation	Dutch Belted Rabbits, pregnant	0, 75, 175, or 350 mg/kg/day	NOEL: 175 mg/kg/day LOEL: 350 mg/kg/day Based on diarrhea, nasal discharge, and death	Rodwell et al., 1980b (MRID 00046363)
Gavage	CD Rats	0, 300, 1,000, or 3,500 mg/kg/day	NOAEL: 1,000 mg/kg/day (fetotoxicity and maternal toxicity), 3,500 mg/kg/day (teratogenicity) Based on breathing, activity, diarrhea, stomach hemorrhages, weight gain, physical appearance, mortality and ossification of sternebrae in fetuses	Rodwell et al., 1980a; Cited as Monsato Co., 1980 in U.S. EPA 1986
Gavage on days 6-19 of gestation	CD Rats, pregnant	0, 300, 1,000, or 3,500 mg/kg/day (98.7% pure)	NOEL: 1,000 mg/kg/day Maternal and developmental toxicity Based on weight gain, mortality, and fetal weights, viability and ossification of	Farmer et al., 2000b

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
			sternebrae	
POEA by gavage on days 6-15 of gestation	CD Rats, pregnant	0,15, 100, or 300 mg/kg/day	NOEL: 15 mg/kg/day Based on food consumption, body weight gain	Farmer et al., 2000b
Phosphate ester neutralized POEA by gavage on days 6-15 of gestation	CD Rats, pregnant	0, 15, 50, or 150 mg/kg/day	NOEL: 50 mg/kg/day Based on mortality, food consumption, body weight gain	Farmer et al., 2000b
Gavage on days 6-19 of gestation	Charles River COBS CD Rats, pregnant	0, 300, 1,000, or 3,500 mg/kg/day	NOEL: 1,000 mg/kg/day LOEL: 3,500 mg/kg/day Based on diarrhea, body weight, breathing, activity patterns, red matter around the mouth, total implantations/dam, unviable fetuses/dam, and deaths	Rodwell et al., 1980b (MRID 00046362)
Gavage on days 7-16 of gestation	Wistar Rats	0, 250, 500, or 1,000 mg/kg/day	No signs of maternal or developmental toxicity	Moxon, 1996a
Reproductive Toxicity				
60-Day Feeding	Charles River CD Rats	0, 3, 10, or 30 mg/kg/day	No effects on rat survival, body weight, consumption, mating, pregnancy, fertility and gestation length observed	Schroeder and Hogan, 1981
2-Generation Feeding	Sprague-Dawley Rats	0, 100, 500, or 1,500 mg/kg/day	NOEL: 1,500 mg/kg/day (reproductive); 500 mg/kg/day (systemic) LOEL: 1,500 mg/kg/day (systemic) Based on soft stools, food consumption, and body weight	Reyna, 1990 (MRID 41621501)
3-Generation Feeding	Sprague-Dawley Rats	0, 3, 10, or 30 mg/kg/day	NOEL: $\geq$ 30 mg/kg/day Systemic and reproductive toxicity Based on focal tubular dilation of kidney	Street, 1982 (MRID 00105995)
3-Generation Feeding	CD Rats	0, 3, 10, or 30 mg/kg/day	No effects on any reproductive parameters	Farmer et al., 2000a

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
Feeding	CD Rats	0, 2,000, 10,000, or 30,000 ppm (97.7 % pure)	NOAEL: 10,000 ppm (740 mg/kg/day) Systemic and reproductive toxicity LOAEL: 30,000 ppm (2268 mg/kg/day) Based on body weight and litter size	Farmer et al., 2000a
Mutagenicity				
Allium anaphase-telophase assay, glyphosate	Allium	1,440 or 2,880 µg/L	No effect	Rank et al., 1993
Allium anaphase-telophase assay, Roundup	Allium	1,440 or 2,880 µg/L	Statistically significant increase in chromosome aberrations	Rank et al., 1993
In vitro lymphocyte cultures, glyphosate	Bovine	17-70 µM	Statistically significant increase of structural aberrations, sister chromatid exchanges, and G6PD activity	Lioi et al., 1998a
Rec-assay, with and without metabolic activation	*B. subtilis* H17 (rec+) and M45 (rec-)	Not provided	No effect, based on increases in mutations	Shirasu et al., 1978 (MRID 00078619)
Gene mutation assay in a Hypoxanthine – Guanine – Phosphoribosyl Transferase (HGPRT) assay, with and without metabolic activation	Chinese hamster ovary (CHO) cells	Not provided	No mutagenic response observed up to limit of cytotoxicity	Li et al., 1983a (MRID 00132681)
Sex-linked recessive lethal (SLRL), Roundup	Drosophila larvae	1 ppm	High frequency of lethals in larval spermatocytes and in spermatogonia	Kale et al., 1995
Sex-linked recessive lethal (SLRL), Pondmaster	Drosophila larvae	0.1 ppm	High frequency of lethals in laraval spermatocytes and in spermatogonia	Kale et al., 1995

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
Reverse mutation assays, with and without metabolic activation	*E. coli* WP2 hcr and *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Not provided	No effect, based on increases in mutations	Shirasu et al., 1978 (MRID 00078619)
In vitro lymphocyte cultures, glyphosate	Human	5.0, 8.5, 17.0, or 51.0 µM	Dose-related increase in the percent of aberrant cells and an increase of SCE/cell	Lioi et al., 1998b
SCE in human lymphocytes *in vitro*, Roundup	Human	0.25, 2.5, or 25 mg/mL	Statistically significant increase ($p<0.001$) in SCE at 0.25 and 2.5 mg/mL; no lymphocyte growth at highest dose	Vyse and Vigfusson, 1979; and Vigfusson and Vyse, 1980
Bone marrow micronucleus assay, Roundup	Mice	133 or 200 mg/kg	No clastogenicity	Rank et al., 1993
Erythrocyte micronuclei (MN) assay, Roundup	Mice	0.5 mL (two injections in 24 hours)	No MN induction	Grisolia, 2002
Structural Chromosomal Aberration Assay	Sprague-Dawley Rats	1 g/kg (single i.p. dose)	No significant effects, based on clastogenic (chromosome-damaging) effect in the bone marrow cells	Li et al., 1983b (MRID 00132683)
Gene mutation assay in an Ames Test, with and without metabolic activation	*Salmonella typhimurium,* strains TA98, TA100, TA1535, and TA1537	Not provided	No response, based on increases in reverse mutations	Kier et al., 1978 (MRID 00078620)
Plate incorporation assay, presence or absence of Aroclor induced S9 mix, Roundup	*Salmonella typhimurium*	360, 720, 1,081, or 1,440 µg/plate	Slight but significant number of revertants at 360 µg/plate for TA98 (w/o S9) and at 720 µg/plate for TA100 (w/ S9)	Rank et al., 1993
Alkaline SCG assay (24-hour exposure), Roundup	Tadpole (*Rana catesbeiana*)	1.69, 6.75, or 27 mg/L	Significant increases in DNA damage at 6.75 mg/L ($p<0.05$) and 27 mg/L ($p<0.001$), compared with controls, no significant increase in DNA damage at 1.69 mg/L	Clements et al., 1997
Erythrocyte	*Tilapia*	50, 100, or 200	Statistically significant	Grisolia, 2002

Table L-20. Summary of Toxicology Studies Included in USDA (2003) and U.S. EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
micronuclei (MN) assay, Roundup	*rendalli*	mg/kg	induction of MN frequencies at all doses	
Frequency of micronucleated cells, glyphosate	*Vicia faba*	35, 70, 105, 140, 350, 700, 1,050, or 1,400 µg/g soil	No genotoxicity	De Marco et al., 1992
Metabolism				
Radiolabeled ^{14}C-glyphosate administered orally	Sprague-Dawley Rats	10 mg/kg, single or repeated	No significant change in metabolism, distribution or excretion, based on absorption and excretion rates	Ridley and Mirly, 1981 (MRID 40767101) and Howe et al., 1988 (MRID 40767102)
Radiolabeled ^{14}C-glyphosate injected	Sprague-Dawley Rats	1,150 mg/kg (single i.p. dose)	Rapidly eliminated from bone marrow and plasma, based on radioactivity measurements	Ridley et al., 1983 (MRID 00132685)

[a] All of the study summaries were derived from USDA (2003) and U.S. EPA (1993). The original primary author citations are included for the purpose of reference. In order to obtain the full citation for these studies, please refer to USDA (2003) and U.S. EPA (1993).

Appendix L-4. Application Rates for Herbicides Recommended for Use on Glyphosate-Tolerant Alfalfa

Table L-21. Honcho®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	**Value**	**Units**	**Reference**
Max AR	2	quarts a.e./acre	Monsanto, 2007b
Percent AI	0.41	unitless	Monsanto, 2007b
Density	1.1655	g/cm3	Monsanto, 2007a
Mass conversion	0.002204623	lb/g	Constant
Volume conversion	946.352946	cm3/quart	Constant
Final AR	1.993946622	lb AI/acre	Equation

Table L-22. Honcho Plus®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	**Value**	**Units**	**Reference**
Max AR	2	quarts a.e./acre	Monsanto, 2007d
Percent AI	0.41	unitless	Monsanto, 2007d
Density	1.1655	g/cm3	Monsanto, 2007c
Mass conversion	0.002204623	lb/g	Constant
Volume conversion	946.352946	cm3/quart	Constant
Final AR	1.993946622	lb AI/acre	Equation

Note: The density value came from the product MSDS. There appears to be a typo on this sheet. It was assumed that the density and specific gravity values would be comparable and that the density of Honcho Plus would be comparable to the density of a similar product, Honcho.

Table L-23. Roundup Original Max®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	**Value**	**Units**	**Reference**
Max AR	44	oz a.e./acre	Monsanto, 2007e
Percent AI	0.487	unitless	Monsanto, 2007e
Density	1360	kg/m3	Monsanto, 2006
Mass conversion	2.204622622	lb/kg	Constant
Volume conversion	2.95735E-05	m3/oz	Constant
Final AR	1.900019095	lb AI/acre	Equation
Specific gravity = Product density/Water density			
Parameter	**Value**	**Units**	**Reference**
Specific gravity	1.36	unitless	Monsanto, 2006
Water density	1000	kg/m3	Constant
Product density	1360	kg/m3	Equation

Note: Density was not provided on label or MSDS sheet. Density was calculated using the provided specific gravity value of 1.36 using the equation Density = Mass/Volume.

Table L-24. Roundup Ultra MaxII®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	**Value**	**Units**	**Reference**
Max AR	44	oz a.e./acre	Monsanto, 2004; Monsanto, 2005c
Percent AI	0.488	unitless	Monsanto, 2004
Density	1360	kg/m3	Equation
Mass conversion	2.204622622	lb/kg	Constant
Volume conversion	2.95735E-05	m3/oz	Constant
Final AR	1.903920572	lb AI/acre	Equation
Specific gravity = Product density/Water density			
Parameter	**Value**	**Units**	**Reference**
Specific gravity	1.36	unitless	Monsanto, 2003
Density of water	1000	kg/m3	Constant
Density of product	1360	kg/m3	Equation

Note: Density was not provided on label or MSDS sheet. Density was calculated using the provided specific gravity value of 1.36 using the equation Density = Mass/Volume.

Table L-25. Roundup Weather Max®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	**Value**	**Units**	**Reference**
Max AR	44	oz a.e./acre	Monsanto, 2007f; Monsanto, 2005b
Percent AI	0.488	unitless	Monsanto, 2007f
Density	1360	kg/m3	Monsanto, 2005a
Mass conversion	2.204622622	lb/kg	Constant
Volume conversion	2.95735E-05	m3/oz	Constant
Final AR	1.903920572	lb AI/acre	Equation
Specific gravity = Product density/Water density			
Parameter	**Value**	**Units**	**Reference**
Specific gravity	1.36	unitless	Monsanto, 2005a
Density of water	1000	kg/m3	Constant
Density of product	1360	kg/m3	Equation

Note: Density was not provided on label or MSDS sheet. Density was calculated using the provided specific gravity value of 1.36 using the equation Density = Mass/Volume.

Appendix L-5. Reference Doses for "Other Chemicals"

Table L-26. Summary of RfDs for "Other Chemicals"

Chemical Name	Reference Dose (Oral)	Reference
2,4-D	Acute dietary (Females 13-49 years of age): 0.025 mg/kg/day Acute dietary (General population including infants and children): 0.067 mg/kg/day Chronic dietary (All populations): 0.005 mg/kg/day	EPA RED, 2005: http://www.epa.gov/oppsrrd1/REDs/24d_red.pdf
Acifluorfen	0.013 mg/kg/day (based on a 2-generation reproduction rat study)	EPA IRIS, 1987: http://www.epa.gov/ncea/iris/subst/0192.htm
Amitrole	Not established	EPA RED, 1996: http://www.epa.gov/oppsrrd1/REDs/0095red.pdf
Atrazine	Acute Dietary: 0.1 mg/kg/day (based on a developmental toxicity study in rat & rabbit) Intermediate and Chronic: 0.018 mg/kg/day (based on a six-month LH surge study in rat)	EPA RED, 2006: http://www.epa.gov/oppsrrd1/REDs/atrazine_combined_docs.pdf
Benefin	0.3 mg/kg/day (based on a dog chronic oral bioassay)	EPA IRIS, 1987: http://www.epa.gov/ncea/iris/subst/0133.htm
Bromoxynil	0.015 mg/kg/day (based on 12-month-chronic oral toxicity study in dogs using bromoxynil phenol)	EPA RED, 1998: http://www.epa.gov/oppsrrd1/REDs/2070red.pdf
Clodinafop	For clodinafop-propargyl: Acute dietary (females 13-50 years of age): 0.05 mg/kg/day (based on a developmental toxicity study in rats) For clodinafop-propargyl: Acute dietary (general population including infants and children): 0.25 mg/kg/day (based on a developmental toxicity study in rabbits) For clodinafop-propargyl: Chronic dietary (all populations): 0.0003 mg/kg/day (based on a chronic toxicity study in rats)	EPA Pesticide Fact Sheet, 2000: http://www.epa.gov/opprd001/factsheets/clodinafop.pdf
Clopyralid	Chronic: 0.5 mg/kg/day (based on a 2-year rat feeding study)	Federal Register, 1997: http://www.epa.gov/EPA-PEST/1997/March/Day-12/p5875.htm

Table L-26. Summary of RfDs for "Other Chemicals"

Chemical Name	Reference Dose (Oral)	Reference
Cyanazine	Not available (NA)	NA
Dicamba	Acute dietary (All populations): 1.0 mg/kg/day (based on acute neurotoxicity in rats) Chronic dietary (All populations): 0.45 mg/kg/day (based on multi-generation reproduction study in rats)	EPA RED, 2006: http://www.epa.gov/oppsrrd1/REDs/dicamba_red.pdf
Diquat	Diquat cation: Chronic: 0.005 mg/kg/day (based on chronic toxicity study in dogs)	EPA RED, 1995: http://www.epa.gov/oppsrrd1/REDs/0288.pdf
Ethalfluralin	0.04 mg/kg/day (based on a one-year oral dog study)	EPA RED, 1995: http://www.epa.gov/oppsrrd1/REDs/2260.pdf
Fenoxaprop	For fenoxaprop-ethyl: Chronic: 0.0025 mg/kg/day (based on a 2-generation rat reproductive study)	Federal Register, 1998: http://www.epa.gov/EPA-PEST/1998/April/Day-22/p10395.htm
Flucarbazone	For flucarbazone-sodium: Acute: 3.0 mg/kg/day (based on a developmental toxicity study in rabbits) For flucarbazone-sodium: Chronic: 0.36 mg/kg/day (based on a one-year dog feeding study)	EPA Pesticide Fact Sheet, 2000: http://www.epa.gov/opprd001/factsheets/flucarbazone.pdf
Fluchloralin	NA	NA
MCPA	Acute (General population): 0.05 mg/kg/day (based on a rat developmental study with MCPA DMAS) Acute (Females 13-50 years old): 0.04 mg/kg/day (based on a rat developmental study with MCPA 2-EHE) Chronic: 0.0044 mg/kg/day (based on a chronic toxicity and carcinogenicity study in rats)	EPA RED, 2004: http://www.epa.gov/oppsrrd1/REDs/mcpa_red.pdf
Metribuzin	Chronic dietary: 0.013 mg/kg/day (based on a two-year feeding study)	EPA RED, 1997: http://www.epa.gov/oppsrrd1/REDs/0181red.pdf
Metsulfuron	For metsulferon methyl: 0.3 mg/kg/day (based on a 2-year rat study)	Federal Register, 1998: http://www.epa.gov/fedrgstr/EPA-PEST/1998/March/Day-19/p7141.htm

Table L-26. Summary of RfDs for "Other Chemicals"

Chemical Name	Reference Dose (Oral)	Reference
MSMA	For all MMAs: Acute: 0.1 mg/kg/day (based on a chronic toxicity dog study) For all MMAs: Chronic: 0.03 mg/kg/day (based on a chronic toxicity rat study)	EPA RED, 2006: http://www.epa.gov/oppsrrd1/REDs/organic_arsenicals_red.pdf
Paraquat	Paraquat cation: Chronic: 0.0045 mg/kg/day (based on 1-year dog feeding study)	EPA RED, 1997: http://www.epa.gov/oppsrrd1/REDs/0179.pdf
Pendimethalin	Chronic: 0.10 mg/kg.day	EPA RED, 1997: http://www.epa.gov/oppsrrd1/REDs/0187red.pdf
Simazine	Acute dietary (females 13-49 years of age): 0.3 mg/kg/day (based on a developmental study in rats) Chronic dietary (all populations): 0.018 mg/kg/day (based on a 6-month LH surge study in rat with atrazine)	EPA RED, 2006: http://www.epa.gov/oppsrrd1/REDs/simazine_red.pdf
Thifensulfuron	For thifensulfuron methyl: Acute dietary (Females 13-50 years of age): 1.59 mg/kg/day (based on a developmental oral toxicity study in rats) For thifensulfuron methyl: Chronic dietary (All populations): 0.20 mg/kg/day (based on a combined chronic/carcinogenicity oral toxicity study in rats)	Federal Register, 2004: http://www.epa.gov/EPA-PEST/2004/September/Day-17/p20983.htm
Tralkoxydim	Acute: 0.3 mg/kg/day (based on a rat developmental study) Chronic: 0.005 mg/kg/day (based on a chronic toxicity study in dogs)	Federal Register, 2005: http://www.epa.gov/EPA-PEST/2005/June/Day-22/p12076.htm
Triallate	Acute (General population including infants and children): 0.60 mg/kg/day (based on an acute neurotoxicity study) Acute (Females 15-30 years): 0.05 mg/kg/day (based on a developmental study in rats) Chronic noncancer: 0.025 mg/kg/day (based on a 2-year chronic toxicity/carcinogenicity study in rats)	EPA RED, 2000: http://www.epa.gov/oppsrrd1/REDs/2695.pdf
Triasulfuron	0.01mg/kg/day (based on a 2-year mouse feeding/carcinogenicity study)	EPA IRIS, 1991: http://www.epa.gov/ncea/iris/subst/0510.htm

Table L-26. Summary of RfDs for "Other Chemicals"

Chemical Name	Reference Dose (Oral)	Reference
Tribenuron	For tribenuron methyl: Chronic: 0.008 mg/kg/day (based on a 1-year dog feeding study) For tribenuron methyl: Acute: 0.20 mg/kg/day (based on rabbit and rat development studies)	Federal Register, 2004: http://www.epa.gov/fedrgstr/EPA-PEST/2004/July/Day-07/p15208.htm
Trichlopyr	0.05 mg/kg/day (based on a 2-generation reproduction study in rats)	EPA RED, 1997: http://www.epa.gov/oppsrrd1/REDs/2710red.pdf
Trietazine	NA	NA
Trifluralin	Chronic: 0.024 mg/kg/day (based on a one-year feeding study in dogs)	EPA RED, 2004: http://www.epa.gov/oppsrrd1/REDs/0179.pdf