Appendix M. Health and Safety Risks to Field Workers

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Health and Safety Risks to Field Workers

Executive Summary

In an effort to assess the potential health and safety risks to field workers from increased glyphosate use in agriculture due to the proposed deregulation of glyphosate-tolerant alfalfa by the U.S. Department of Agriculture (USDA) in 2005, a screening-level occupational health risk assessment was conducted for glyphosate use on glyphosate-tolerant (GT) alfalfa. As defined by the U.S. Environmental Protection Agency (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). 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 workers are not at risk of adverse health effects associated with acute or chronic dermal exposure to glyphosate. More details on the toxicity and risk of glyphosate are discussed in this technical report.

Glyphosate is a broad spectrum herbicide. It is a systemic, post-emergence herbicide widely used on both agricultural commodities and nonagriculture sites. Glyphosate absorbs directly through plant leaves and spreads rapidly throughout the plant. The use of surfactants enables greater leaf penetration. Glyphosate's mode of action is as a potent and specific inhibitor of the enzyme 5-enolpyruvylshikimate 3-phosphate synthase. This enzyme is located in the shikimate pathway and is essential for the biosynthesis of aromatic amino acids and other aromatic compounds in algae, higher plants, bacteria, fungi, and apicomplexian parasites. The shikimate pathway is absent in mammals.

Glyphosate is among the most widely used pesticides by volume in the United States. While additional glyphosate products may be used, five products are recommended for use on GT alfalfa. The five herbicides are Monsanto products and include: Honcho®, Honcho Plus®, Roundup Original MAX®, Roundup WeatherMAX®, and Roundup Ultra MAX II®. Glyphosate products can be formulated to have different concentrations of glyphosate acid per gallon of product. To improve handling, performance, and concentration, the glyphosate acid is formulated as a salt compound. The term acid equivalent (a.e.) refers to the weight of the glyphosate acid, which is herbicidally active, while the term active ingredient (a.i.) is the weight of the glyphosate acid plus the salt.

The EPA and the States (usually that State's agriculture office) register or license pesticides for use in the United States. EPA receives its authority to register pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act. Glyphosate was registered for use as an herbicide within the United States through EPA. EPA's toxicological database on glyphosate is considered adequate and complete (US EPA, 1993, 2006). Based on these data, glyphosate is considered to be a toxicologically low-risk herbicide (Cerdeira and Duke, 2006). According to the

Reregistration Eligibility Decision (RED) document for glyphosate (US EPA, 1993), glyphosate is of relatively low oral and dermal acute toxicity. For this reason, glyphosate has been assigned to Toxicity Categories III and IV for these effects (i.e., Toxicity Category I indicates the highest degree of acute toxicity, and Category IV the lowest). 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. With regard to subchronic and chronic toxicity, one of the more consistent effects of exposure to glyphosate is loss of body weight. This observed weight loss may be consistent with experimental data indicating glyphosate's mechanism of action. Other general and nonspecific signs of toxicity from subchronic and chronic exposure to glyphosate include changes in liver weight, blood chemistry (may suggest mild liver toxicity), liver pathology, and pituitary weight (USDA, 2003). Glyphosate is not considered a carcinogen; it has been classified by EPA as a Group E carcinogen (evidence of noncarcinogenicity for humans) (US EPA, 1993, 2006).

There are two types of worker exposure scenarios assessed in this report. The first are general worker scenarios in which workers have chronic dermal exposure to glyphosate via one of three typical pesticide application methods: directed foliar, broadcast foliar, or aerial. Chronic dermal screening level exposure estimates ranged from 0.9 ppb (i.e., µg/kg) to160 ppb for directed foliar application, from 1.32 ppb to 302 ppb for broadcast foliar application, and from 0.48 ppb to 160 ppb for aerial application. Note that while directed foliar application is applied by backpack, which is a typical application method for forestry uses, but not for GT alfalfa production, it has been included here for completeness.

Central, lower, and upper bound chronic dermal screening hazard quotient (HQ) estimates were all under 1, suggesting that workers exposed to herbicides recommended for use on GT alfalfa via directed foliar, broadcast foliar, or aerial application methods are not at risk of adverse effects associated with chronic dermal exposure to glyphosate. HQs ranged from 0 to 0.8 for directed foliar application, from 0.001 to 0.15 for broadcast foliar application and from 0 to 0.08 for aerial application. The most exposed workers were those using a broadcast foliar application method. The upper bound HQ was 0.15.

In addition to general worker scenarios, accidental exposure scenarios are also assessed in this report. Accidental exposure scenarios result in workers' acute exposure to glyphosate. There are two accidental exposure scenarios assessed in this report, including an accidental spill on the worker's hands or an accidental spill on the worker's legs. Acute dermal screening level exposure estimates from a spill on the worker's hands ranged from 4.44 ppb to 50.5 ppb. Acute dermal screening level exposure estimates from a spill on the worker's legs ranged from 10.9 to 124 ppb.

Central, upper, and lower bound screening HQs were all under 1, suggesting that workers who accidentally spill herbicides recommended for use on GT alfalfa on hands or legs are not at risk of adverse effects associated with acute dermal exposure to glyphosate. HQs for a spill on the hands ranged from 0.002 to 0.025. HQs for a spill on the legs ranged from 0.005 to 0.062. The most exposed workers were those who spilled glyphosate on the legs. The upper bound HQ was 0.06.

1.0 Introduction

In June 2005, the USDA approved the use of Roundup Ready® alfalfa, the only commercially available genetically engineered alfalfa on the market. Roundup Ready® alfalfa is resistant to the herbicide glyphosate. This means that it is able to survive applications of glyphosate, the a.i. in the Monsanto Company's trademark herbicide, Roundup®. Monsanto produced this glyphosate-tolerant (GT) alfalfa in partnership with the largest alfalfa seed company, Forage Genetics International. The transgene responsible for glyphosate tolerance was first introduced in soybeans in 1996 and has since been commercialized in several other crops (e.g., corn, canola, and cotton). In order to determine health and safety risks to field workers in contact with GT alfalfa, an occupational risk assessment must consider the toxicology and exposure potential associated with herbicides containing glyphosate that may be used on the crop.

1.1 Herbicides

There are several herbicide products containing glyphosate that are recommended for use on GT alfalfa. These products include: Roundup Original Max®, Roundup Weather Max®, and Roundup Ultra Max II® (Monsanto, 2008). According to Greenbook, an online database that partners with chemical manufacturers such as Monsanto to provide information about agricultural products, Honcho® and Honcho Plus® are also recommended for use on GT alfalfa (Greenbook, 2008). Each of these products contains between 41 and 48 percent glyphosate (Monsanto 2004; 2007b; 2007d; 2007f; 2007e). Consideration of other ingredients in the end-use products (EUPs) is beyond the scope of this exposure assessment. For purposes of this analysis, exposure estimates of glyphosate are presented as opposed to exposure estimates of the EUPs because toxicological data required to assess risk were not available for the EUPs at the time of this analysis.

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 increased more than six-fold between 1992 and 2002, to become the most used herbicide in the United States. In 1997, it was listed on the Agency of Toxic Substances and Disease Registry's (ATSDR) 100 most frequently released substances (ATSDR, 1997). Uncertainty exists over whether glyphosate use has increased as a result of GT crops, as well as whether other (more toxic and/or persistent) herbicides have increased or decreased as a result or will in the future. See appendix L, *Health and Safety Risks from Increased Glyphosate and Other Chemical Use on Humans (Exclusive of Field Workers)*, for additional background on this issue.

Biomonitoring studies confirm that agricultural workers who apply glyphosate to crops internalize some of the chemical (Curwin et al., 2007; Mandel et al., 2005). EPA (1993) determined in its RED for glyphosate that the chemical may be classified as either a Category III (i.e., slightly toxic; slightly irritating) or Category IV (i.e., practically nontoxic; not an irritant) toxicant. Toxicity and occupational exposure data exist for glyphosate, and the remainder of this occupational assessment utilizes these data to estimate exposure and risk to field workers.

Given the expected increase in glyphosate use that would result from deregulation, a screening-level human health risk assessment for farm workers was conducted using highly conservative assumptions. The results of this assessment should not be construed as indicating the likelihood of actual adverse health effects.

1.2 Gene Product

The expressed gene product in GT alfalfa is a protein, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), derived from a soil bacterium, Agrobacterium sp. CP4 strain, thus called CP4 EPSPS. The protein is a single polypeptide that is 455 amino acids long and structurally and functionally similar to the native plant EPSPS enzymes. The herbicide glyphosate inhibits an essential step in aromatic amine synthesis in plants. The CP4 EPSPS protein is not inhibited by the herbicide glyphosate; thus any plant with the protein is resistant to glyphosate application.

1.3 Conventional Crop

Conventional alfalfa has been used for animal feed for decades. Alfalfa is also consumed by humans (e.g., sprouts, dietary supplements, and herbal teas). Pollen from alfalfa may be a minor contributor to some respiratory allergic diseases such as asthma, but the risk to human health is minimal. Monsanto does not allow GT alfalfa to be planted for sprouts (Hubbard, 2008).

1.4 Methodology

This analysis addresses exposure to the herbicide glyphosate. Thus, the remainder of this analysis focuses on the chemical and physical properties of glyphosate and its toxicological data. These data, in combination with data specific to the occupational scenarios, are used to conduct an occupational risk assessment for workers exposed to glyphosate. The result of the assessment is an estimate of potential risks associated with occupational exposures to glyphosate due to increased use of glyphosate and deregulation of GT alfalfa.

To support the occupational assessment, literature searches of glyphosate toxicity and exposure were conducted in the open literature using the literature search strategy presented in appendix M-2 of this technical report. This occupational assessment is not a comprehensive summary of all of the available information and does not cite all of the available literature. As USDA (2003) determined, an all inclusive and detailed review of all of the available literature 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: EPA's (1993) RED on glyphosate, EPA's (2006) Glyphosate Human Health Risk Assessment for Proposed Use on Indian Mulberry and Amended Use on Pea, Dry, and USDA's (2003) human health and ecological risk assessment on glyphosate.

Additionally, for the exposure assessment, the application rate of glyphosate on GT alfalfa was determined by collecting the use rates on GT alfalfa from labels of the five products recommended for use on GT alfalfa mentioned previously. It can be expected that other formulations for glyphosate herbicide could and may be used on GT alfalfa. However, this analysis focuses only on the products recommended for use on GT alfalfa.

2.0 Overview of Glyphosate

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_2H_2) groups may 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 2007b). This and other surfactants are added to the herbicide formulations to increase leaf penetration.

See sections 1 and 2 of appendix L, *Health and Safety Risks to the General Population*, for additional background on glyphosate.

3.0 Occupational Risk Assessment

3.1 Hazard Identification

This occupational risk assessment focuses on risks associated with exposure to herbicides recommended for use on GT alfalfa, all of which contain the a.i. 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 worker exposure estimates 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 worker exposure estimates are compared to health benchmarks to determine the potential for adverse health effects associated with occupational exposures to glyphosate.

See section 3.1 of appendix L, *Health and Safety Risks to the General Population*, for a detailed description of the hazard from glyphosate formulations.

3.2 Exposure Assessment

As mentioned in section 2, there are five EUPs containing glyphosate that are recommended for use on Roundup Ready® alfalfa. These products include: Roundup Original Max®, Roundup Weather Max®, and Roundup Ultra Max II® (Monsanto, 2008). Two additional products, Honcho® and Honcho Plus®, are also listed in Greenbook, an online database that partners with chemical manufacturers such as Monsanto to provide information about agricultural products (Greenbook, 2008). Each of these products contains between 41 and 48 percent glyphosate (Monsanto, 2004; Monsanto, 2007a; Monsanto, 2007c; Monsanto, 2007d). For purposes of this

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.

3.2.1 Routes of Exposure

Workers exposed to glyphosate in products used to treat GT alfalfa may be exposed via dermal or inhalation routes of exposure. However, EPA determined in its RED for glyphosate that the chemical is nonvolatile (US EPA, 1993). For this reason, the inhalation route of exposure is not considered in this analysis. This analysis also does not consider incidental oral exposure to glyphosate for workers. For further discussion of oral exposure for the general public, please refer to the technical report: *Health and Safety Risks to the General Population* (appendix L).

EPA's RED for glyphosate indicated that occupational exposure to glyphosate has resulted in eye and skin irritation (US EPA, 1993). Accordingly, EPA recommended that personal protective equipment be worn by mixers, loaders, and applicators of products containing glyphosate. EPA set the restricted entry interval (REI) for glyphosate at 12 hours due to the potential for acute dermal toxicity and skin and eye irritation immediately after products have been applied. However, it cannot be assumed that the recommendation for personal protective equipment and the REI will be honored universally. A subsequent EPA (2006) assessment of glyphosate for use on Indian mulberry and dried peas stated that the 12 hour REI has not been implemented universally. Thus, this exposure analysis and resulting risk characterization does not assume that personal protective equipment is worn, nor does it assume that workers wait 12 hours before entering a treated field.

3.2.2 Application Rates

Typical single application rates of products containing glyphosate range from less than 1.5 pounds of glyphosate a.i. per acre up to 3.75 pounds of glyphosate a.i. per acre; maximum label rate for a single application on GT alfalfa is 1.55 pounds of glyphosate a.e. (Monsanto, Undated). Application rates were determined using specific product labels for each EUP recommended for use on GT alfalfa. Application rates on these products were presented in volume (i.e., quarts or ounces) of a.i. 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 M-1 and M-2).

Equation M-1

$$Density = Mass / Volume$$

thus,

Equation M-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/m3 (See equations M-3 and M-4).

Equation M-3

Specific gravity = Product density / Water density

thus,

Equation M-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.i. (i.e., glyphosate) reported by the product label was considered in the exposure equation (See equation 3). The percent of glyphosate in EUPs ranged from 41 and 48.8 percent (See table L-1 in appendix L).

Equation M-5

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

Application rates of the five EUP recommended for use on GT alfalfa are presented in table M-1. Please refer to appendix M-4 in this technical report for further detail on the information used to calculate application rates.

Table M-1. Application Rates of EUPs Recommended for Use on GT Alfalfa

Product	Single Use Application Rate	Reference
Roundup Original Max®	1.9 lb a.i./acre	Monsanto, 2006b; Monsanto, 2007e
Roundup Weather Max®	1.9 lb a.i./acre	Monsanto, 2005a; Monsanto, 2005b; Monsanto, 2007f
Roundup Ultra Max II®	1.9 lb a.i./acre	Monsanto, 2004; Monsanto 2005c; Monsanto 2003
Honcho®	2.0 lb a.i./acre	Monsanto, 2007a; Monsanto, 2007b
Honcho Plus®	2.0 lb a.i./acre	Monsanto, 2007c; Monsanto, 2007d

3.2.3 Occupational Exposure Scenarios

Occupational exposure to glyphosate may be categorized as general worker exposure or as accidental worker exposure. General worker exposure estimates are based on the assumption of continuous contact with a chemical. Accidental worker exposure estimates are based on specific events that may not involve exposure over extended time periods.

3.2.3.1 General Worker Exposure Scenarios

In general, pesticides are applied using one of three application methods: direct foliar, broadcast foliar, and aerial. According to Monsanto, the vast majority of Roundup® brand herbicides are applied using ground equipment, which could be for either direct or foliar broadcast applications (Monsanto Undated). Chronic general worker exposure scenarios are described by USDA (2003) and corresponding exposure algorithms are provided in a calculations worksheet presented to USDA by SERA (2006). Regardless of the application method, general worker absorbed dermal doses ($AD_{general}$) of glyphosate may be estimated by multiplying the amount of the chemical handled per day by the absorbed dose rate (See equation M-6). The amount of chemical handled per day as well as the number of acres treated in a day may vary greatly (Acquavella et al., 2006). Using SERA's (2006) algorithms, the amount of the chemical handled

per day (*Amnt*) is the product of the application rate and the number of acres treated per day (See equation M-7). The number of acres treated per day (*ATD*) may be calculated by multiplying the number of hours spent applying the chemical by the number of acres treated per hour) (SERA, 2006) (See equation M-8).

Equation M-6

$$AD_{general} = Amnt*ADR$$

Where:

$AD_{general}$	=	absorbed dermal dose (mg/kg BW/day)
Amnt	=	amount of chemical handled per day (lb/day)
ADR	=	absorbed dermal dose rate (mg/kg BW per lb applied)

Equation M-7

$$Amnt = AR*ATD$$

Where:

Amnt	=	amount of chemical handled per day (lb/day)
AR	=	application rate (lb/acre)
ATD	=	acres treated per day (acres/day)

Equation M-8

$$ATD = Hrs*APH$$

Where:

ATD	=	acres treated per day (acres/day)
Hrs	=	hours of application per day (hours/day)
APH	=	acres treated per hour (acres/hour)

Absorbed dose rates (*ADR*) for different application scenarios were estimated by SERA (2001). These rates will be considered constants for the present analysis. Central, upper, and lower bound rate estimate for directed foliar, broadcast foliar, and aerial application methods may be found in table M-2. USDA (2003) validated these rates for direct foliar applications by analyzing urine samples of agricultural workers exposed to glyphosate. Using biomonitoring data in addition to application rates and urinary output and bodyweight defaults, exposure rates were calculated. Three worker studies were examined and the results indicated that the upper range (0.01 mg/kg body weight per pound applied) is likely to overestimate exposure as all of the rates based on biomonitoring data were much lower. Therefore, these absorbed dose rates represent conservative assumptions that will be protective of the general worker population.

Table M-2. Absorbed Dose Rates (in mg/kg body weight per pound of active ingredient applied)

Exposure Scenario	Central	Lower	Upper	Reference
Directed foliar	0.003	0.0003	0.01	SERA, 2001
Broadcast foliar	0.0002	0.00001	0.0009	
Aerial	0.00003	0.000001	0.0001	

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 5 EUPs recommended for use GT alfalfa (See table M-2). This rate is consistent with the range of application rates typical of Monsanto herbicides

containing glyphosate (Monsanto Undated). (It is unlawful to apply glyphosate to GT alfalfa at a rate higher than 1.55 pounds of glyphosate a.e.)

Default values may also be used for the hours of application per day (*Hrs*) and the number of acres treated per hour (*APH*). USDA estimated that workers may spend between 6 (lower bound) and 8 (upper bound) hours applying chemicals per day (USDA, 1989). USDA (1989) also suggested default values for the number of acres treated per hour. These values differ depending on the pesticide application method. Workers using the direct foliar application method may cover approximately 0.625 acres/hour (range: 0.25 to 1 acre/hour). Workers using the broadcast foliar method may cover approximately 16 acres/hour (range: 11 to 21 acres/hour). Workers using the aerial application method may cover approximately 70 acres/hour (range: 40 to 100 acres/hour).

Central, lower, and upper bound screening exposure estimates were calculated for the three different application scenarios. Results are presented in table M-3. Central estimates for the three different application exposure scenarios ranged from 2.63E-02 to 4.48E-02 mg/kg body weight per day. Upper estimates ranged from 1.6E-01 to 3.02E-01 mg/kg body weight per day.

Table M-3. Chronic Screening Exposure Estimates for General Worker Exposure Scenarios (in mg/kg body weight per day)

Exposure Scenario	Central Estimate	Lower Estimate	Upper Estimate
Directed foliar	2.63E-02	9.00E-04	1.60E-01
Broadcast foliar	4.48E-02	1.32E-03	3.02E-01
Aerial	2.94E-02	4.80E-04	1.60E-01

3.2.3.2 Accidental Worker Exposure Scenarios

Accidental exposure scenarios may involve multiple routes of exposure, including oral and inhalation in addition to dermal exposure. However, due to a dearth of validated quantitative models to estimate oral and/or inhalation dose to workers, this analysis focuses on accidental dermal exposures only. There are many possible accidental exposure scenarios that could be considered. The scenarios included in this analysis are an accidental spill on the hands of the worker and an accidental spill on the lower legs of the worker. This analysis assumes that the worker was not wearing personal protective equipment on the hands or legs, thus the chemical contacted the skin directly. Acute scenarios for accidental worker exposure are described by USDA (2003) and corresponding exposure algorithms are provided in a calculations worksheet presented to USDA by SERA (2006).

The worker's absorbed dermal dose from a spill on the hands or lower legs (AD_{spill}) may be estimated by dividing the product of the absorbed dermal dose from a chemical spill on the hands or legs and the proportion of the chemical absorbed by the body weight of the worker (see equation M-9). The amount of the chemical deposited on the skin (*Amnt*) may be estimated by multiplying the amount of liquid that adheres to the worker's skin, the surface area of the workers hands or legs, and the concentration of the chemical in the solution (equation M-10). The proportion of the chemical absorbed over the time that the worker is exposed (*Prop*) may be estimated using equation M-11.

Equation M-9

$$AD_{spill} = Amnt*Prop/BW$$

Where:

AD_{spill}	=	absorbed dermal dose from spill on hands or legs (mg/kg)
Amnt	=	amount of chemical deposited on skin (mg)
Prop	=	proportion absorbed over exposure duration (unit less)
BW	=	body weight of worker (kg)

Equation M-10

$$Amnt = L*SA*Conc$$

Where:

SkinDep	=	amount of chemical deposited on skin (mg)
L	=	amount of liquid that adheres to the worker's skin (mL/cm^2)
SA	=	surface area of the worker's hands or legs (cm^2)
Conc	=	concentration of the chemical in the solution (mg/mL)

Equation M-11

$$Prop = 1-exp(-ka*ED)$$

Where:

PropAbs	=	proportion absorbed over exposure duration (unit less)
ka	=	dermal absorption rate (per hour)
ED	=	exposure duration (hours)

Default values were used for some of the variables used to characterize accidental exposure to workers. The body weight (*BW*) of the worker is assumed to be 71.8 kg which is the mean adult body weight recommended by the EPA's Exposure Factors Handbook (US EPA, 1997). The amount of liquid that can adhere to the skin (*L*) at a given time was estimated by Mason and Johnson (1987). According to their analysis, 0.008 mL of liquid can adhere to 1 cm^2 of skin. Surface area (*SA*) estimates of the worker's hands and lower legs are from EPA's Dermal Exposure Assessment: Principles and Applications report (1992). It is assumed that the worker's hands have a surface area of 840 cm^2 and that the lower legs have a surface area of 2070 cm^2. The concentration of the chemical in the solution (*Conc*) was found on the label of each EUP. The maximum concentration in solution is 540 mg/mL and the minimum is 365 mg/mL. Central and lower limit exposure estimates assume the minimum concentration while upper limit exposure estimates assume the maximum concentration in solution. Assumptions regarding the dermal absorption rate (*ka*) are based on a study by Wester et al. (1991) on the ability of glyphosate to bind to the skin, absorb, and distribute in tissue. Dermal absorption rates range from 1.3E-04 to 1.0E-03 per hour. Finally, it is assumed that a worker's skin or lower legs would be exposed for a period of one hour (*ED*).

Central, lower, and upper bound exposure estimates were calculated for two accidental exposure scenarios in which the worker's hands or lower legs are exposed for one hour. Results are presented in table M-4. Central estimates for the accidental exposure scenarios ranged from 1.40E-02 to 3.45E-02 mg/kg body weight per day. Upper estimates ranged from 5.05E-02 to 1.24E-01 mg/kg body weight per day.

Table M-4. Acute Screening Exposure Estimates for Accidental Worker Exposure Scenarios (in mg/kg body weight per day)

Exposure Scenario	Central Estimate	Lower Estimate	Upper Estimate
Spill on hands	1.40E-02	4.44E-03	5.05E-02
Spill on legs	3.45E-02	1.09E-02	1.24E-01

3.2.4 Summary

3.2.4.1 General Worker Exposure Scenarios

General worker screening level exposure estimates from direct foliar application of herbicides recommended for use on GT alfalfa ranged from 9.00E-04 to 1.60E-01 mg/kg body weight per day. General worker screening level exposure estimates from broadcast foliar application of herbicides recommended for use on GT alfalfa ranged from 1.32E-03 to 3.02E-01 mg/kg body weight per day. General worker screening level exposure estimates from aerial application of herbicides recommended for use on GT alfalfa ranged from 4.80E-04 to 1.60E-01 mg/kg body weight per day. Section 3.4 places these exposure estimates in the context of a glyphosate-specific human health benchmark in order to estimate risk of potential adverse effects associated with chronic dermal exposure to glyphosate.

3.2.4.2 Accidental Worker Exposure Scenarios

Screening level exposure estimates from an accidental spill on a worker's hands ranged from 4.44E-03 to 5.05E-02 mg/kg body weight per day. Exposure estimates from an accidental spill on a worker's legs ranged from 1.09E-02 to 1.24E-01 mg/kg body weight per day. Section 3.4 places these exposure estimates in the context of a glyphosate-specific human health benchmark in order to estimate risk of potential adverse effects associated with acute dermal exposure to glyphosate.

3.3 Dose-Response Assessment

3.3.1 Overview

A Reference Dose (RfD) is defined as a level of exposure that will not result in any adverse effects in any individual. The oral RfD value for glyphosate proposed by EPA's Office of Pesticide Programs (EPA OPP) 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 no adverse effect level (NOAEL) of 175 mg/kg/day (Rodwell et al., 1980). The RfD of 2 mg/kg/day was derived by dividing the NOAEL by an uncertainty factor of 100 (i.e., 10 for sensitive individuals and 10 for species-to-species extrapolation) and rounding the result to one significant figure (US EPA, 2006, 2002, 1993).

3.3.2 Existing Guidelines

This section reviews two chronic RfDs for glyphosate proposed by EPA OPP and the World Health Organization's (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

(US EPA, 1993). EPA's Integrated Risk Information System (IRIS) also derived an RfD for glyphosate of 0.1 mg/kg/day (US EPA, 1990). 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 from this study was 10 mg/kg/day and an uncertainty factor of 100 was applied to derive an RfD of 0.1 mg/kg/day.

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) dosed the diets of male and female rats daily with glyphosate for 26 months (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). 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.

EPA's 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 2,000 to 6,000 mg/kg reported in experimental mammals. 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 was rapidly excreted from the body. Therefore, it may be assumed that duration of exposure is not a crucial parameter in assessing the toxicity of glyphosate (USDA, 2003).

The data for experimental animals were further analyzed using a categorical regression analysis in the next step of assessing the dose-severity relationships. The analysis correlates categorical responses with factors that may 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 may be overly protective by a factor of 10 or greater.

3.3.4 Susceptible Populations

In developmental studies in rats and rabbits and reproductive studies in rats, glyphosate exhibited no evidence of increased qualitative and quantitative susceptibility. 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 (US EPA, 2006).

3.3.5 RfD Values Used in Risk Assessment

The glyphosate database is large, complex, and open to many interpretations. The Joint Food and Agricultural Organization of the United Nation/WHO on Pesticides Residues recommended an ADI for glyphosate of 0.3 mg/kg *per se*. 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. However, 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, EPA OPP's Reference Dose Peer Review Committee recommended an oral reference dose for glyphosate of 2 mg/kg/day for long-term exposures (USDA, 2003). EPA ODW recommended an oral reference dose of 2 mg/kg/day for short-term exposures. As a result, the same RfD is recommended for both short- (i.e., acute) and long-term (i.e., chronic) exposures. Due to a lack of significant dose-response data for glyphosate, this approach was deemed appropriate (USDA, 2006; US EPA, 1993, 2002). Glyphosate endpoints for this risk assessment are summarized in table M-5 below.

EPA did not include an RfD for dermal exposure to glyphosate (1993). However, following the lead of USDA (2003), a dermal RfD of 2 mg/kg/day was used for short- and long-term dermal exposures.

Table M-5. Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Health Risk Assessments (US 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)	2.0 mg/kg/day [US EPA does not maintain a dermal RfD; however, USDA (2003) used an acute and chronic RfD to conduct a dermal exposure assessment for occupational workers]	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		

3.4 Risk Characterization

3.4.1 Overview

As discussed in section 3.2, workers may be exposed to herbicides recommended for used on GT alfalfa via dermal contact with treated crops. Workers may also be exposed accidentally via spills to hands or legs. Glyphosate is considered a Category IV dermal toxicant and may cause slight skin irritation (US EPA, 1993, 2006).

3.4.2 Risk Characterization

To determine if workers are 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, USDA (2003) used a dermal reference dose (RfD) for acute (i.e., accidental) and chronic (i.e., general) exposure scenarios for glyphosate of 2 mg/kg of body weight per day. This means that individuals with dermal 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 M-12). 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 greater than 1, adverse health effects are possible. However, an HQ exceeding 1 does not indicate that adverse effects are certain to occur. Since glyphosate is considered a Group E carcinogen (i.e., signifies noncarcinogenicity in humans) (EPA, 1993), an analysis of cancer risk was not conducted.

Equation M-12.

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

Where:

HQ	=	Hazard quotient (unit less)
Exposure	=	Estimated exposure dose (mg/kg BW per day)
RfD	=	Reference dose (mg/kg BW per day)

Risk Characterization for General Worker Exposure Scenarios

Chronic dermal exposure estimates for three occupational scenarios in which a worker applies glyphosate using a directed foliar, broadcast foliar, or aerial application method were presented in section 3.2. Results are summarized in table M-6. Please refer to the calculations worksheet submitted with this report for further explanation of exposure calculations.

Table M-6. Chronic Dermal Screening Exposure Estimates by Method of Application (in mg/kg BW per day)

Scenario	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Directed Foliar	2.63E-02	9.00E-04	1.60E-01	1
Broadcast Foliar	4.48E-02	1.32E-03	3.02E-01	2
Aerial	2.94E-02	4.80E-04	1.60E-01	3

Chronic dermal exposure estimates were compared to the chronic dermal RfD of 2 mg/kg of body weight per day. Results are presented in table M-7. Please refer to the calculations worksheet submitted with this report for further explanation of hazard quotient calculations.

Table M-7. Chronic Dermal Screening HQs for General Worker Exposure Scenarios

Scenario	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
Directed Foliar	0.0131	0.0005	0.0800	2	7
Broadcast Foliar	0.0224	0.0007	0.1512		
Aerial	0.0147	0.0002	0.0800		

3.4.2.2 Risk Characterization for Accidental Worker Exposure Scenarios

Acute dermal exposure estimates for two spill scenarios in which a worker spills glyphosate on the hands or legs were presented in section 3.2. Results are summarized in table M-8. Please refer to the calculations worksheet submitted with this report for further explanation of exposure calculations.

Table M-8. Acute Dermal Screening Exposure Estimates by Type of Spill (in mg/kg BW per day)

Scenario	Central Estimate	Lower Estimate	Upper Estimate	Worksheet
Spill on hands	1.40E-02	4.44E-03	5.05E-02	4
Spill on legs	3.45E-02	1.09E-02	1.24E-01	5

Acute exposure estimates were compared to the acute dermal RfD of 2 mg/kg of body weight per day. Results are presented in table M-9. Please refer to the calculations worksheet submitted with this report for further explanation of hazard quotient calculations.

Table M-9. Acute Dermal Screening HQs for General Worker Exposure Scenarios

Scenario	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
Spill on hands	0.007	0.002	0.025	2	7
Spill on legs	0.017	0.005	0.062		

3.4.3 Summary of Results

This analysis assumes that workers exposed to glyphosate may have chronic or acute dermal exposure. The scientific literature demonstrates that general worker exposure estimates vary greatly because the amount of chemical handled per day and the number of acres treated in a day differs from scenario to scenario. Central, lower, and upper bound exposure and risk calculations are intended to capture some of this variability.

3.4.3.1 Chronic Dermal Risk Characterization

Central, lower, and upper bound screening HQs for general worker exposure scenarios do not suggest that workers are at risk of adverse effects associated with chronic dermal exposure to glyphosate. HQs ranged from 0 to 0.8 for directed foliar application, from 0.001 to 0.15 for

broadcast foliar application and from 0 to 0.08 for aerial application. The most exposed workers were those using a broadcast foliar application method. The upper bound HQ was 0.15.

3.4.3.2 Acute Dermal Risk Characterization

Central, lower, and upper bound screening HQs for acute worker exposure scenarios do not suggest that workers are at risk of adverse effects associated with acute dermal exposure to glyphosate. HQs for a spill on the hands ranged from 0.002 to 0.025. HQs for a spill on the legs ranged from 0.005 to 0.062. The most exposed workers were those who spilled glyphosate on the legs. The upper bound HQ was 0.06.

3.5 Summary of Findings

The use of currently registered pesticide products containing glyphosate in accordance with the labeling will not pose unreasonable occupational risks or adverse effects to. 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 and chronic toxicity by the dermal route of exposure. Glyphosate is considered a Category IV dermal toxicant and is expected to cause only slight skin irritation.

General or chronic worker exposure estimates from directed foliar application of herbicides recommended for use on GT alfalfa ranged from 9.00E-04 mg/kg/day to 1.60E-01 mg/kg/day. Chronic exposure estimates from broadcast foliar application ranged from 1.32 E-03 to 3.02E-01 mg/kg/day. Chronic exposure estimates from aerial application ranged from 4.80E-04 to 1.60E-01 mg/kg/day.

Central, upper, and lower bound chronic screening HQs were all under 1, suggesting that workers using these methods of application to apply herbicides recommended for use on GT alfalfa are not at risk of adverse effects associated with dermal exposure to glyphosate. HQs for directed foliar application ranged from 0 to 0.8. HQs for broadcast foliar application ranged from 0.001 to 0.15. HQs for aerial application ranged from 0 to 0.08. The most exposed workers were those using a broadcast foliar application method. The upper bound HQ was 0.15.

Accidental or acute worker exposure estimates from an accidental spill of herbicides recommended for use on GT alfalfa on the hands ranged from 4.44E-03 mg/kg/day to 5.05E-02 mg/kg/day. Acute worker exposure estimates from an accidental spill on the legs ranged from 1.09E-02 mg/kg/day to 1.24E-01 mg/kg/day.

Central, upper, and lower bound screening HQs were all under 1, suggesting that workers who accidentally spill herbicides recommended for use on GT alfalfa on hands or legs are not at risk of adverse effects associated with acute exposure to glyphosate. HQs for a spill on the hands ranged from 0.002 to 0.025. HQs for a spill on the legs ranged from 0.005 to 0.062. The most exposed workers were those who spilled glyphosate on the legs. The upper bound HQ was 0.06.

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.

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WHO. (1996). The WHO recommended classification of pesticides by hazard and guidelines to classification 1996–1997. Geneva, World Health Organization, International Programme on Chemical Safety (WHO/PCS/96.3). *(As cited in WHO, 2005).*

Williams, G.M., Kroes, R., Munro, I.C. (2000). Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. *Regul Toxicol Pharmacol*. 31(2 Pt 1):117-65. *(As cited in USDA, 2003).*

Appendix M-2. Literature Search

1.0 Literature Search Strategy

1.1 Purpose

The purpose of this literature search is to locate references about the health and safety risks for field workers from increased glyphosate use. These references will be used to examine the literature on potential health and safety risks for field workers.

We propose that the following DIALOG databases be included in the search:

The following DIALOG databases will be included in the search:

File 5: BIOSIS
File 6: NTIS
File 34: SciSearch
File 41: Pollution Abstracts
File 40: Enviroline
File 72: EMBASE
File 76: Environmental Sciences
File 79: Aqualine
File 98: General Science Abstracts
File 117: Water Resources Abstracts
File 144: PASCAL
File 154: MEDLINE
File 156:ToxFile
File 245: WATERNET™
File 250: CAB Abstracts
File 266: Federal Research In Progress (FEDRIP)
File 399: CA SEARCH®: Chemical Abstracts®

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

1.2 Scope of Search

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

The following list will be retrieved and expanded upon.

1.3 Strategy Overview

A list of search parameters is listed below.

1.4 Synonyms

- Glyphosate
- Glyphosate, isopropylamine salt
- Glyphosate, sodium salt
- Glyphosate, potassium
- *N*-(phosphonomethyl) glycine
- Roundup®
- Rodeo®
- Aqua Star

- Glyphosate, ammonium
- Glyphosate, sulfosate
- Shackle®
- Roundup Ultra®

1.5 Keywords

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

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 will include the following (when available):

Author(s). Publication Year. Title. Source Document Name, Volume, Page Numbers.
Abstract
Descriptors/Identifiers (*i.e.*, keywords and subject headings)

Literature Search Results

```
File  10:AGRICOLA 70-2008/Apr
         (c) format only 2008 Dialog
  File 154:MEDLINE(R) 1990-2008/Jun 02
```

```
        (c) format only 2008 Dialog
  File 266:FEDRIP 2008/Feb
        Comp & dist by NTIS, Intl Copyright All Rights Res
  File 156:ToxFile 1965-2008/May W4
        (c) format only 2008 Dialog
  File  55:Biosis Previews(R) 1993-2008/May W4
        (c) 2008 The Thomson Corporation
  File   6:NTIS 1964-2008/Jun W1
        (c) 2008 NTIS, Intl Cpyrght All Rights Res
  File 117:Water Resources Abstracts 1966-2008/Mar
        (c) 2008 CSA.
  File  41:Pollution Abstracts 1966-2008/May
        (c) 2008 CSA.
  File  40:Enviroline(R) 1975-2008/Apr
        (c) 2008 Congressional Information Service
  File  44:Aquatic Science & Fisheries Abstracts 1966-2008/Mar
        (c) 2008 CSA.
  File  76:Environmental Sciences 1966-2008/Jun
        (c) 2008 CSA.
  File 144:Pascal 1973-2008/May W4
        (c) 2008 INIST/CNRS
  File 162:Global Health 1983-2008/Apr
        (c) 2008 CAB International
  File  50:CAB Abstracts 1972-2008/Apr
        (c) 2008 CAB International
  File  73:EMBASE 1974-2008/May 30
        (c) 2008 Elsevier B.V.

S1      28882   GLYPHOSATE OR PHOSPHONOMETHYL()GLYCINE OR
ROUNDUP OR RODEO
             OR AQUA()STAR OR SHACKLE OR GLYPHOSPHATE
S2      14787   RN=1071-83-6 OR PHOSPHONOMETHYLIMINOACETIC()ACID
OR SILGLIF OR PONDMASTER
S3      11254   (S1 OR S2)/2000:2008
S4    8322013   ACUTE OR SUBACUTE OR CHRONIC OR SUBCHRONIC OR
INGEST? OR I-
             NHAL? OR AVERAGE()DAILY()INTAKE OR DOSE OR DOSAGE
OR DIETARY
S5    5982530   TOXIC? OR (HEALTH OR ADVERSE OR SIDE)(3N)(EFFECT
OR EFFECTS
              OR RISK OR RISKS OR IMPACT OR IMPACTS) OR
NEUROTOXIC? OR GEN-
             OTOXIC? OR IMMUNOTOXIC?
S6    5900953   CANCER? OR CARCINO? OR TUMOR? OR NEOPLAS?
S7    7007833   DERMA? OR SKIN OR EYE OR EYES OR OCCULAR? OR
REPRODUCTI? OR
```

EMBRYRO? OR TERATOL? OR TERATOGEN? OR IRRITAT? OR IRRITANT OR NEUROLOG?
S8 10892095 FERTILITY OR INFERTIL? OR MUTAGEN? OR MUTAT? OR SENSITIZ? -
OR OCCUPATIONAL OR EXPOS? OR METABOLI?
S9 34112 (FARM OR FIELD OR MIGRANT OR AGRICULTURAL OR PESTICIDE)()W-
ORKER? ? OR FARMWORKER? OR FIELDWORKER? OR FARMHAND? ? OR FIELDHAND? ?
S10 3991193 USAGE()PATTERN? ? OR SPRAY()DRIFT? OR TOLERANCE OR PERSIST-
ENCE OR INHIBITION OR INCIDENTAL OR DEGRADATION OR ALFALFA OR LEACH?
S11 2348875 SAFETY OR SAFE OR POISON? OR INTOXICAT?
S12 4507 S3 AND (S4 OR S5 OR S6 OR S7 OR S8 OR S11)
S13 1122 S12 AND (S9 OR S10)
S20 25773370 HUMAN OR HUMANS
S23 2487202 FARM()(FAMILY OR FAMILIES) OR HOME OR HOMES OR FARMER? ? OR
RANCH OR RANCHER? ? OR WORKER? ? OR WORKMEN OR CHILDREN
S24 2294 S3 AND (S9 OR S10)
S25 5141 (S12 OR S24) NOT (S14 OR S15 OR S21)
S26 740 S25 AND (S23 OR S20)
S27 326 RD S26 (unique items)

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

22/6/16 (Item 16 from file: 73)
0080039478 EMBASE No: 2004224625
Cancer mortality in a cohort of licensed herbicide applicators
May 1, 2004

22/6/18 (Item 18 from file: 73)
0078903517 EMBASE No: 2002067195
Contact *dermatitis* caused by pesticides among banana plantation workers in Panama
March 4, 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*

22/6/31 (Item 31 from file: 73)
0078517319 EMBASE No: 2001123409
Frequency of sister-chromatid exchange among greenhouse farmers *exposed*
to pesticides
April 5, 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

22/6/48 (Item 48 from file: 73)
0078783023 EMBASE No: 2001389406
Protective headgear for midwestern agriculture: A limited wear study
November 17, 2001

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

22/6/53 (Item 53 from file: 154)
15493238 PMID: 14655902
Pesticide use among farmers in the Amazon basin of Ecuador.
Apr *2003*

22/6/55 (Item 55 from file: 154)
16149335 PMID: 15724348
Pesticide patch test series for the assessment of allergic contact
dermatitis among banana plantation workers in panama.
Sep *2004*

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

22/6/60 (Item 60 from file: 73)
0078058968 EMBASE No: 2000108216
Safety of working conditions of *glyphosate* applicators on Eucalyptus
forests using knapsack and tractor powered sprayers
April 3, 2000

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

28/6/18 (Item 18 from file: 162)
0004850526 CAB Accession Number: 20023045993
Aerial herbicide impact on *farmers* in Ecuador.
Publication Year: 2001

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*

28/6/38 (Item 38 from file: 154)
17620883 PMID: 17432331

Coca and poppy eradication in Colombia: environmental and *human* health
assessment of aerially applied *glyphosate*.
2007

28/6/42 (Item 42 from file: 156)
021261 NLM Doc No: CIS/05/00367 Sec. Source ID: CIS/05/00367
Chemical use among *farmers*
2004

28/6/43 (Item 43 from file: 154)
17573764 PMID: 17365078
Chemical *exposure* among NZ *farmers*.
Feb *2007*

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

28/6/64 (Item 64 from file: 154)
16192679 PMID: 15626647
Cancer incidence among *glyphosate*-*exposed* pesticide applicators in
the Agricultural Health Study.
Jan *2005*

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*

28/6/120 (Item 120 from file: 73)
0079340986 EMBASE No: 2003044076
Epidemiologic studies of *occupational* pesticide *exposure* and *cancer*
: Regulatory risk assessments and biologic plausibility
January 1, 2003

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

28/6/223 (Item 223 from file: 55)
0020239571 BIOSIS NO.: 200800286510
Occupational rhinitis is associated with pesticide *exposure* among
commercial pesticide applicators in the agricultural health study
2008

28/6/225 (Item 225 from file: 154)
16192106 PMID: 15596423
Operator *exposure* when applying amenity herbicides by all-terrain
vehicles and controlled droplet applicators.
Jan *2005*

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*

28/6/237 (Item 237 from file: 55)
0019886841 BIOSIS NO.: 200700546582
Parental *occupational* *exposure* to pesticides and the risk of childhood
leukemia in Costa Rica
2007

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

28/6/256 (Item 256 from file: 156)
3971471 NLM Doc No: 15724348
Pesticide patch test series for the assessment of allergic contact
dermatitis among banana plantation *workers* in panama.
Sep *2004*

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*

28/6/258 (Item 258 from file: 156)
4366648 NLM Doc No: 18320729
Pesticide-related *dermatitis* in Saku district, Japan, 1975-2000.
Jan-Mar *2008*

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*

28/6/285 (Item 285 from file: 10)
3817140 22040661 Holding Library: AGL
Safety of working conditions of *glyphosate* applicators on Eucalyptus
forests using knapsack and tractor powered sprayers
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*

28/6/319 (Item 319 from file: 154)
16190994 PMID: 15620861
Vitamins C and E reverse effect of herbicide-induced *toxicity* on
human epidermal cells HaCaT: a biochemometric approach.
Jan 20 *2005*

Appendix M-3. Summary of Toxicology Studies

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US 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) Based on erythema, edema, food consumption, and serum changes	Johnson et al., 1982 (MRID 00098460)
6-Weeks, gelatin capsule administered orally	New Zealand Rabbits, male	$1/10^{th}$ or $1/100^{th}$ 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

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
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 (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
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, 457 or 1,183 mg/kg/day)	NOEL: 8,000 ppm (both sexes), Males: 362 mg/kg/day, Females: 457 mg/kg/day LOEL: 20,000 ppm (both sexes), Males: 940 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	Stout and Ruecker, 1990 (MRID 41643801)
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				

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
18-Month Feeding	CD-1 Mice	0, 150, 750, or 4,500 mg/kg/day	NOEL: 750 mg/kg/day LOEL: 4,500 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	2,000, 8,000, or 20,000 ppm (Males: 89, 362 or 940 mg/kg/day Females: 45, 113 or 1,183 mg/kg/day)	NOAEL: 8,000 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 6-27 of gestation	Dutch Belted Rabbits, pregnant	0, 75, 175, or 350 mg/kg/day	NOEL: $\geq$ 175 mg/kg/day	Rodwell et al., 1980b (MRID 00046363)
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 number of litters and fetuses with ossified 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 1,500 mg/kg/day	NOEL: 500 mg/kg/day LOEL: 1,500 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

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
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 sternebrae	Farmer et al., 2000b
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, inviable fetuses/dam, and deaths	Rodwell et al., 1980 (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)

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
3-Generation Feeding	Sprague-Dawley Rats	0, 3, 10, or 30 mg/kg/day	NOEL: ≥ 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
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 laraval 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
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)

Table M-10. Summary of Toxicology Studies Included in USDA (2003) and US EPA (1993) Reports

Study Type	Species	Dose Range	Result	Primary Author(s)[a]
In vitro lymphocyte cultures, glyphosate	Human	5.0, 8.5, 17.0, or 51.0 µM	Dose-related increase in the percent of abberant 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 micronuclei (MN) assay, Roundup	*Tilapia rendalli*	50, 100, or 200 mg/kg	Statistically significant induction of MN frequencies at all doses	Grisolia, 2002
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 US 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 US EPA (1993).

Appendix M-4. Application Rates for Herbicides Recommended for use on Glyphosate-Tolerant Alfalfa

Table M-11. Honcho®

Final Max AR = Max AR*Percent AI*Product Density*Mass Conversion*Volume Conversion			
Single Application			
Parameter	Value	Units	Reference
Max AR	2	quarts ae/acre	Monsanto, 2007b
Percent AI	0.41	unit less	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 M-12. 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 ae/acre	Monsanto, 2007d
Percent AI	0.41	unit less	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 M-13. 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 ae/acre	Monsanto, 2007e
Percent AI	0.487	unit less	Monsanto, 2007e
Density	1360	kg/m3	Monsanto, 2006b
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	unit less	Monsanto, 2006b
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 M-14. 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 ae/acre	Monsanto, 2004; Monsanto, 2005c
Percent AI	0.488	unit less	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	unit less	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 M-15. 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 ae/acre	Monsanto, 2007f; Monsanto, 2005b
Percent AI	0.488	unit less	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	unit less	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.